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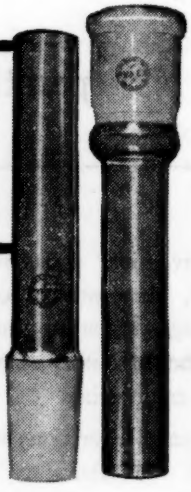

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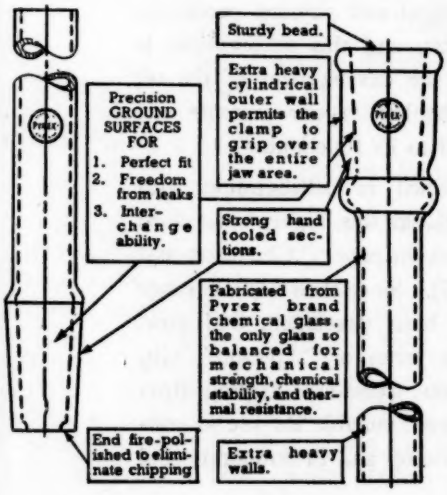
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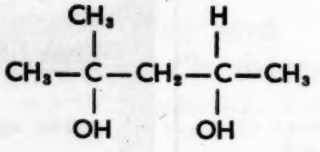

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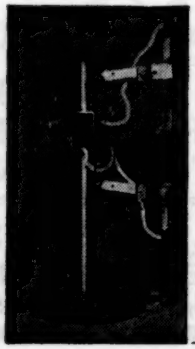

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products of low molecular weight, and this is undoubtedly due to the ready capture of an α-methylenic hydrogen atom by the polymer radical, to give the stable allylic-type radical; *e.g.*,

$$X{\cdot}CH_2{\cdot}CH{:}CH_2 + R \longrightarrow X{\cdot}CH_2{\cdot}CHR{\cdot}\dot{C}H_2 \text{ (Initiation)}$$
$$X{\cdot}CH_2{\cdot}CHR{\cdot}\dot{C}H_2 + X{\cdot}CH_2{\cdot}CH{:}CH_2 \longrightarrow X{\cdot}CH_2{\cdot}CHR{\cdot}CH_2 + \dot{C}HX{\cdot}CH{:}CH_2$$

On the other hand, the typical α-methyl-containing monomers such as methacrylate or methacrylonitrile polymerise easily to high-molecular products because substitution stabilises the propagating radical and α-methylenic abstraction is greatly reduced. Similarly, the highly stable styrene-type radical, $Ph{\cdot}CH{\cdot}CH_2X$, shows little tendency to transfer. In fact, it may be concluded quite generally that substitutents effective in promoting radical stabilisation greatly reduce the probability of monomer chain-transfer.

In solution polymerisation, the solvent may also take part in transfer in a manner analogous to that of monomer transfer discussed above. The activity of the radical may be transferred to the solvent, forming a new radical which may start a fresh chain:

$$\cdot M_n + SH \longrightarrow M_n + S\cdot$$
$$\cdot S + M \longrightarrow M\cdot + HS \text{ or } SM\cdot$$

Mayo has shown (Mayo, *J. Amer. Chem. Soc.*, 1943, **65**, 2324; Gregg and Mayo, Faraday Soc. Discussion, "Labile Molecule," 1947, p. 328) that, if all the new radicals S· start chains, a simple relation exists between the average degree of polymerisation $\bar{P}$ and the chain-transfer coefficient C, viz.,

$$\frac{1}{\bar{P}} = \frac{1}{\bar{P}_0} + C\frac{[SH]}{[M]}$$

where $C = k_s/k_p$ is the ratio of the velocity constant of the reaction, $M_n\cdot + S \xrightarrow[k_s]{} M_n + S\cdot$, to that of the reaction, $M_n\cdot + M \xrightarrow[k_p]{} \dot{M}_{n+1}$, and $\bar{P}_0$ is the average degree of polymerisation in absence of the chain-transfer agent. The chain-transfer coefficient is thus a comparison of the reactivity of the growing polymer radical for reaction with the solvent and with that of the monomer. By using a variety of chain-transfer agents in the same polymeric system it is thus possible to compare the absolute velocities of reaction of a given polymer radical with a series of solvent molecules. Mayo (*loc. cit.*) has shown, from transfer measurements on the styrene radical in a series of hydrocarbons (that is, a measurement of the capacity to supply a hydrogen atom to a substituted benzyl radical), that the ease with which the hydrogen atom can be removed from a carbon atom in methane is increased appreciably by alkyl groups on the carbon atom, greatly by phenyl groups, and still more by an *o*-diphenylene group (fluorene being 1000 times more reactive than *cyclo*hexane). These results show that the increased activity in chain transfer with hydrocarbons is determined by the stability of the solvent-type radical formed, the least activation energy being required to form the most stable radical.

Copolymerisation.—When the material undergoing polymerisation consists of a mixture of two unsaturated monomers, the addition polymer formed is built up from units of each of the monomers. Such a polymer is known as a copolymer. In these mixtures the rate of polymerisation by a radical mechanism is governed by four chain-growth processes, determined by the two types of radical reacting with M_1 and M_2, *viz.*: $M_1\cdot + M_1 \xrightarrow{k_{11}} M_1\cdot$; $M_1\cdot + M_2 \xrightarrow{k_{12}} M_2\cdot$; $M_2\cdot + M_2 \xrightarrow{k_{22}} M_2\cdot$; $M_2\cdot + M_1 \xrightarrow{k_{21}} M_1\cdot$. By the use of the stationary-state method it is possible to derive the copolymerisation equation:

$$\frac{dM_1}{dM_2} = \frac{M_1 r_1 M_1 + M_2}{M_2 r_2 M_2 + M_1}$$

where $r_1 = k_{11}/k_{12}$, and $r_2 = k_{22}/k_{21}$. The equation can be intergrated and from a knowledge of the experimentally determined monomer ratio in the polymer, together with a knowledge of the initial composition of the mixture, the reactivity ratios, r_1 and r_2, can be determined.

Now, the reactivity ratios are the ratios of the rate of addition of a monomer to a radical of its own kind and that of the rate of addition of the second monomer to the same radical. This ratio supplies, therefore, a quantitative measure of the rate of reaction of any radical with another monomer. A monomer reactivity ratio >1 indicates a tendency of the radical to perpetuate its own kind, whilst a ratio <1 indicates a preference for reaction with the other monomer. Thus the relative rate constants of the reactivity of a reference radical with a number of monomers can be determined. Table IV (Mayo, Lewis, and Walling, Faraday Soc. Discussion, "Labile

TABLE IV.

	r_1.	r_2.		r_1.	r_2.
Styrene	1·00	1·00	Vinyl chloride	17	0·02
Butadiene	0·78	—	Vinyl acetate	55	0·01
Methyl methacrylate	0·52	0·46	Vinyl ethyl ether	90	—
Methyl vinyl ketone	0·29	—	Allyl chloride	31	—
Acrylonitrile	0·40	0·04	Allyl acetate	90	0·01
2-Chloroethyl acrylate	0·54	0·10	Maleic anhydride	0·01	0·07
Methyl acrylate	0·75	0·18	Diethyl fumarate	0·30	—
Vinylidene chloride	1·85	0·14	Diethyl maleate	6·52	—
Methallyl chloride	22	—			
Methallyl acetate	71	—			

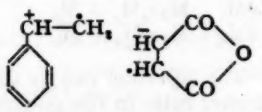
Molecule," 1947, p. 285) shows the relative reactivities of various monomers with the styrene radical. The results, for instance, show that the rate of reaction of the styrene radical with methyl methacrylate is just twice that with styrene momomer, whereas with vinylidene chloride it is about half as fast.

The table shows clearly the specific nature of the reactivity of free radicals. It so happens that the order in which radicals fall is much the same for a number of different radicals, even though the absolute rates may vary greatly from one radical to another. The broad conclusion which follows is that monomers with conjugated vinyl, phenyl, carbonyl, cyano-, or carbalkoxy-groups are considerably more reactive than the monomers without such conjugation. The data show also that the addition of one methyl or one chlorine substituent increases the reactivity of the double bond: methacrylate > acrylate; methacrylonitrile > acrylonitrile; vinylidene chloride > vinyl chloride; methallyl > allyl. It has thus become possible to compile a list (*loc. cit.*) of the ability of substituents R to increase the reactivity of the monomer $CH_2{:}CHR$ towards free radicals, viz., $C_6H_5 > H_2C{:}CH > R{\cdot}CO{\cdot} > N{:}C{\cdot} > RO{\cdot}CO{\cdot} > Br > Cl > R{:}O{\cdot} > R{\cdot}CH_2{\cdot} > H$.

It follows from our previous consideration of resonance stabilisation of radicals that the most reactive double bonds yield the most stabilised and the least reactive radicals, and that the least reactive double bonds yield the most reactive radicals.

The above order of substituents is, therefore, that corresponding to the order of their ability to promote resonance stabilisation of the methyl radical. Thus, $\cdot CH_2{\cdot}CH{:}CH_2$ or $CH_2{\cdot}CH_2{\cdot}C_6H_5$ should be more stabilised and less reactive than $\cdot CH_2Cl$ or $\cdot CH_2{\cdot}CH_2{\cdot}R$, and the free CH_3 should be most reactive. This order agrees with the low reactivity of triphenylmethyl and allyl radicals.

A striking feature of many free radical polymerisations is that, in many pairs, each radical reacts preferentially with the opposite-type radical, giving rise to an alternating effect in the chain. The copolymer formed consists of regularly alternating units of the two polymers, *e.g.*, styrene–maleic anhydride, and styrene–allyl acetate. Maleic anhydride or the maleic esters do not polymerise alone (or with great difficulty to low degrees of polymerisation), but will readily copolymerise with other monomers, such as styrene, and may even accelerate the rate. In many copolymerisations this tendency to alternation is superimposed upon the general activity of monomers in copolymerisation. Two explanations have been advanced to explain the alternation effect. Price (Price, *J. Polymer. Sci.*, 1946, **1** 83; Price and Alfrey, *ibid.*, 1947, **2**, 101) assumed that the effect arises from the difference in polarity of the radical and the double bond, a negative radical being attracted by a positive double bond and vice versa. The other explanation, due to Mayo *et al.* (*loc. cit.*), assumes that special resonance forms are available to the reactants in the transition state, *e.g.*, the double bond of the styrene molecule donates an electron to the maleic anhydride radical, the resulting structures being



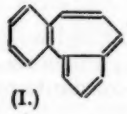
The maleic anhydride portion has become a stable enolate ion, and the styrene portion has now available more resonance structures. Reactions of this type introduce a new feature which is of particular interest since electrostatic influences are not usually encountered among free radical reactions. The general effect of electron availability and the effect of substituents on the charge distribution in radicals are not yet understood and must await further experimental and theoretical developments. Nevertheless, it appears that the main features of radical reactions can be interpreted in terms of the resonance energies and the strength of bonds.

222. *Cyclic Conjugated Polyenes. Part II.* 4 : 5-*Benzazulene.*

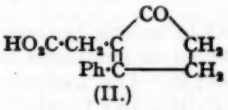
By J. R. Nunn and W. S. Rapson.

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-4 : 5-*benzazulene* has been prepared in 6 stages from 3-phenyl-*cyclo*pent-2-en-1-one-2-acetic acid, and has been dehydrogenated to yield a product characterised as 4 : 5-benzazulene by the formation of *addition compounds* with 1 : 3 : 5-trinitrobenzene and 2 : 4 : 6-trinitrotoluene. In the free state 4 : 5-benzazulene was found to be unstable. An attempt to prepare a methoxy-4 : 5-benzazulene *via* the *cyclo*dehydration of 1-(3-m-*methoxyphenyl*-n-*propyl*)cyclo*pentan*-2-*one* failed.

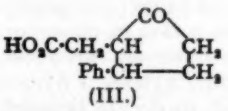
4 : 5-Benzazulene (I), in which a benzene ring is fused to the seven-membered ring of the azulene structure, has been synthesised. For this purpose the *ethyl* ester of 3-phenyl*cyclo*pent-2-en-1-one-2-acetic acid (II) (Robinson, *J.*, 1938, 1390) was hydrogenated, and the *acid*



(I.)

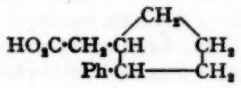


(II.)

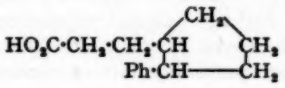


(III.)

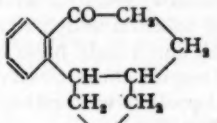
(III) derived from the product further reduced by Huang-Minlon's modification of the Wolff–Kishner method (*J. Amer. Chem. Soc.*, 1946, **68**, 2487). Attempts to effect the conversion in one stage by application of the Clemmensen method failed, the product under all conditions being a mixture of the derived lactones. 2-Phenyl*cyclo*pentane-1-acetic acid (IV) yielded 2-*phenyl*cyclo*pentane*-1-*propionic acid* (V) in good yield by the Arndt–Eistert method, and the



(IV.)

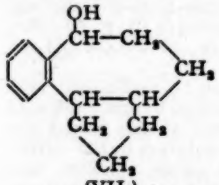


(V.)

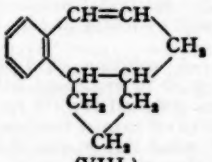


(VI.)

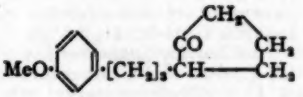
ring closure of the acid chloride of this acid to yield *octahydro*-4 : 5-*benzazul*-6-*one* (VI) was carried out in carbon disulphide solution in the presence of aluminium chloride. (VI) afforded the corresponding *carbinol* (VII) on reduction with sodium and ethanol, and, since the crystalline character of this carbinol caused practical difficulties in its dehydrogenation by the method previously described (Part I, this vol., p. 825), it was dehydrated with potassium hydrogen sulphate to yield the liquid 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-4 : 5-*benzazulene* (VIII). When (VIII), in the vapour phase, was subjected to the action of palladium–charcoal in a vacuum at 350° an intensely blue liquid was produced. A deep blue substance, characterised as 4 : 5-benzazulene, was extracted from this condensate by means of phosphoric acid, and the unchanged material could be recycled through the dehydrogenation apparatus. In solution 4 : 5-benzazulene was intensely blue, and it formed well-defined crystalline *complexes* with



(VII.)



(VIII.)



(IX.)

1 : 3 : 5-trinitrobenzene and 2 : 4 : 6-trinitroluene which were very stable and easily obtained in a pure condition. All attempts to obtain this benzazulene in a pure condition for analysis, however, have so far failed. It rapidly underwent change (polymerisation ?) to give an insoluble green substance, a reaction which seemed to be catalysed by sunlight. This change occurred even when the operations were carried out under carbon dioxide. This behaviour is in contrast to that of 1 : 2-benzazulene (Part I, *loc. cit.*) which is a stable compound, and it is intended to attempt the synthesis of 5 : 6-benzazulene in order to discover whether this instability arises from fusion of the benzene ring to the seven-membered ring of the azulene structure.

Despite its apparent instability, the production of 4 : 5-benzazulene by a high-temperature dehydrogenation process is indicative of some degree of aromatic character. Further, the

formation and stability of molecular complexes with 1 : 3 : 5-trinitrobenzene and 2 : 4 : 6-trinitrotoluene indicate that the 4 : 5-benzazulene structure has high polarisability and hence considerable electron mobility. The effects of polarising substituents on the stability of 4 : 5-benzazulene are worthy of further study, and experiments are planned from this point of view.

In an attempt to synthesise a methoxy-4 : 5-benzazulene and at the same time to elaborate another 4 : 5-benzazulene synthesis, the *cyclo*dehydration of 1-(3-*m*-methoxyphenyl-*n*-propyl)-*cyclo*pentan-2-one (IX) has been explored. 3-*m*-Methoxyphenyl-*n*-propyl iodide, prepared according to the directions of Robinson and Schlittler (*J.*, 1935, 1288), was condensed with ethyl potassio*cyclo*pentan-2-one-1-carboxylate to give a high yield of 1-carbethoxy-1-(3-*m*-methoxyphenyl-*n*-propyl)*cyclo*pentan-2-one. This substance was hydrolysed with barium hydroxide to give 1-(3-*m*-methoxyphenyl-*n*-propyl)adipic acid, which would not crystallise. When this acid was distilled in the presence of barium hydroxide it afforded 1-(3-*m*-methoxyphenyl-*n*-propyl)*cyclo*pentan-2-one (IX).

The action of phosphoric oxide on (IX) in boiling benzene or toluene produced no change. When, however, this substance was subjected to prolonged treatment with phosphoric oxide, in boiling xylene, a hydrocarbon was isolated. The analysis and physical constants made it difficult to decide between the formulæ $C_{14}H_{22}$ and $C_{15}H_{24}$.

It is certain that it contained a benzene nucleus since :

(*a*) The ultra-violet absorption spectrum shows an intense maximum (log ε 3·13) at 352 mμ. Benzene and all alkylated benzenes have their maxima in this region (Baly and Collie, *J.*, 1905, **87**, 1332).

(*b*) In a series of test-tube reactions the hydrocarbon was nitrated and the nitro-compound, so formed, reduced to the corresponding amine. When this amine was diazotised and the diazo-solution added to a strongly alkaline solution of β-naphthol, a deep red colour developed, which could only have occurred had the original substance contained a benzene nucleus.

Despite these observations, however, no characteristic product was obtained in attempts to degrade it with either potassium permanganate or chromic oxide and this substance remains unidentified.

Aryl*cyclo*pentenoneacetic acids such as (II) appear to constitute more convenient starting materials for the preparation of substituted 4 : 5-benzazulenes.

Experimental.

(M. p.s are uncorrected.)

3-*Phenyl*cyclo*pentan*-1-*one*-2-*acetic Acid* (III).—3-Phenyl*cyclo*pent-2-en-1-one-2-acetic acid (135 g.) (Robinson, *loc. cit.*) was esterified by refluxing in absolute ethanol (500 c.c.), containing sulphuric acid (15 c.c.), for 4 hours. On being worked up the mixture afforded the *ester* (126 g.), b. p. 166—167°/0·5 mm., which solidified on standing. Recrystallisation from light petroleum (b. p. 30—50°) gave large colourless prisms with a hexagonal cross-section, m. p. 46–47° (Found : C, 73·7; H, 6·7. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%). This ester (126 g.) was hydrogenated in ethanol solution in the presence of palladium–calcium carbonate catalyst. Removal of the catalyst and distillation afforded 3-*phenyl*cyclo*pentan*-1-*one*-2-*acetate* (126 g.) as an oil, b. p. 160—162°/1 mm., $n_D^{15\cdot5°}$ 1·5234 (Found : C, 73·0; H, 7·2. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Hydrolysis of this ester yielded 3-*phenyl*cyclo*pentan*-1-*one*-2-*acetic acid* (111 g.) as an oil which solidified on standing. Recrystallisation from light petroleum (b. p. 50—60°) gave stout colourless prisms, m. p. 129—130° with softening at 120° (Found : C, 71·8; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·5%).

2-*Phenyl*cyclo*pentane*-1-*acetic Acid* (IV).—A solution of 3-phenyl*cyclo*pentan-1-one-2-acetic acid (55 g., 0·25 mol.), potassium hydroxide (42·4 g., 0·76 mol.) and 50% (w/w) hydrazine hydrate (59 c.c.) in 2 : 2′-dihydroxydiethyl ether (310 c.c.) was refluxed for 1·5 hours. At the end of this period the condenser was removed and enough water distilled off to raise the temperature of the solution to 195—200°, where it was maintained for 3 hours. The cooled liquor was then poured into water, acidified, and the liquid acid (49 g.) extracted with ether. For the purpose of characterisation a small quantity of this acid was esterified with ethanol containing a trace of sulphuric acid to give the *ethyl* ester, b. p. 119—121°/0·5 mm. (Found : C, 77·9; H, 8·4. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%).

2-*Phenyl*cyclo*pentane*-1-*propionic Acid* (V).—Phosphorus pentachloride (8·2 g., 0·038 mol.) was added to a solution of 2-phenyl*cyclo*pentane-1-acetic acid (7·8 g., 0·038 mol.) in dry benzene (85 c.c.). The mixture was stirred till solution was complete and then the benzene and phosphorus oxychloride were distilled off under vacuum on the water-bath. Distillation of the residue afforded the acid chloride (6·3 g.), b. p. 120—122°/0·1 mm. This acid chloride (6·3 g., 0·028 mol.), in a little ether, was added dropwise to a vigorously-stirred anhydrous solution of diazomethane (3·6 g., 0·085 mol.) in ether which was kept between −5° and 0°. A vigorous evolution of nitrogen began immediately, and after standing for half an hour at this temperature the solution was allowed to warm to room temperature and then set aside overnight. The next morning the ether and excess diazomethane were removed under reduced pressure on a water-bath kept initially at 20° and finally at 30°, leaving a viscous yellow residue of diazo-ketone, which was dissolved in absolute ethanol (75 c.c.) and warmed on a water-bath kept at 80°.

A slurry of silver oxide, obtained from 10% silver nitrate solution (12 c.c.), in absolute ethanol (30 c.c.) was then added, in 6 equal portions, to the solution of diazoketone over a period of 2 hours. The solution was then refluxed gently for half an hour, but even after this treatment some unreacted diazoketone remained. Reaction was complete after the solution had been left overnight. A little charcoal was added to the mixture which was then boiled and filtered hot. Distillation gave *ethyl 2-phenylcyclopentane-1-propionate* (6·0 g., 86% of theory calculated on acid chloride), b. p. 132—133°/0·4 mm., $n_D^{14\cdot6°}$ 1·5140 (Found: C, 77·8; H, 8·6. $C_{16}H_{22}O_2$ requires C, 78·0; H, 8·9%). Hydrolysis of this ester gave the acid as pale yellow plates from light petroleum (b. p. 30—50°), m. p. 77—78° (softens 76°) (Found: C, 76·9; H, 8·2. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%).

Octahydro-4 : 5-benzazul-6-one (VI).—The acid chloride of 2-phenylcyclopentane-1-propionic acid was prepared by adding the acid (45 g., 0·2 mol.) in dry benzene (200 c.c.) dropwise to a vigorously-stirred solution of phosphorus pentachloride (43 g., 0·2 mol.) in dry benzene (300 c.c.). The benzene and phosphorus oxychloride were then removed under reduced pressure with heating on a water-bath. In order to remove the last trace of phosphorus oxychloride a further 20 c.c. of benzene was added and again removed under reduced pressure. This acid chloride, in pure carbon disulphide (400 c.c.), was added dropwise to a vigorously-stirred mixture of finely-ground aluminium chloride (30·4 g.) and carbon disulphide (2400 c.c.) over a period of 6 hours, the solution being in a bath kept at 40—50°. After all the acid chloride had been added the mixture was refluxed for a further 3 hours. The dark red-brown carbon disulphide solution was then poured on crushed ice and hydrochloric acid. The undissolved complex in the flask was similarly treated and the ketone extracted from it with ether. The combined extracts were then washed with alkali and water and dried (Na_2SO_4). Evaporation of the solvent and distillation of the residue yielded the *ketone* (28 g., 68% of theory calculated on acid) as an oil, b. p. 126—127°/0·2 mm., which immediately solidified. Recrystallisation from light petroleum (b. p. 20—40°) gave clusters of needles, m. p. 65·5—67° with previous softening (Found: C, 84·55; H, 8·1. $C_{14}H_{16}O$ requires C, 84·0; H, 8·1%). The *semicarbazone* separated from ethyl acetate in well-formed colourless plates, m. p. 202—204° (Found: C, 70·2; H, 7·35. $C_{15}H_{19}ON_3$ requires C, 70·0; H, 7·4%).

Octahydro-4 : 5-benzazul-6-ol (VII).—Sodium (16·3 g.) was added in small pieces over a period of an hour to a boiling solution of octahydro-4 : 5-benzazul-6-one (16·3 g.) in absolute ethanol (163 c.c.). When all the sodium had dissolved the solution was cooled, diluted with water, and the carbinol isolated by means of ether. The dried neutral extract yielded, on distillation, *octahydro-4 : 5-benzazul-6-ol* (11·23 g.) as a very viscous colourless oil, b. p. 120—125°/0·2 mm., which crystallised on standing. It gave very fine, colourless needles from light petroleum (b. p. 50—60°), m. p. 119—119·5° (softens 110°) (Found: C, 82·7; H, 9·0. $C_{14}H_{18}O$ requires C, 83·1; H, 9·0%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro-4 : 5-benzazulene* (VIII).—Octahydro-4 : 5-benzazul-6-ol (3·0 g.) was heated with potassium hydrogen sulphate (4·3 g.) at 180—190° for 1·5 hours. The mixture was then cooled, extracted with ether, and the ethereal solution washed with alkali and water and dried. Distillation of this extract gave a colourless oil, b. p. 99—100°/0·2 mm., $n_D^{16°}$ 1·5818, $d_{16°}^{16°}$ 1·018, $[R]_D$ 60·34 (calc. 58·38) (Found: C, 90·5; H, 8·7. $C_{14}H_{16}$ requires C, 91·3; H, 8·7%).

Dehydrogenation of Hexahydro-4 : 5-benzazulene.—The apparatus and procedure previously described (Part I, *loc. cit.*) were used to dehydrogenate this hydrocarbon. The optimum temperature was 350°. The deep blue distillate from the reaction was taken up in light petroleum (b. p. 20—40°) and extracted with ice-cold 85% phosphoric acid. This phosphoric acid extract was yellow and displayed an intense green fluorescence. After being thoroughly washed with ice-cold petroleum, the phosphoric acid extract was poured into a mixture of ice and peroxide-free ether. Evaporation of the solvent from the dry neutral ethereal solution afforded 4 : 5-benzazulene as a viscous blue oil. The petroleum solution (after the phosphoric acid extraction) was washed and dried and the solvent evaporated. The residue was then subjected to further dehydrogenation. Proceeding in this fashion 6·7 g. of hexahydrobenzazulene afforded, by successively extracting and recycling, 1·86 g. of crude 4 : 5-benzazulene. The 1 : 3 : 5-*trinitrobenzene* addition compound separated from ethanol in deep brown needles, m. p. 160—161° (Found: C, 61·9; H, 3·5. $C_{20}H_{13}O_6N_3$ requires C, 61·4; H, 3·35%). The 2 : 4 : 6-*trinitrotoluene* addition compound separated from ethanol in black-brown needles, m. p. 120° (Found: C, 62·7; H, 4·15. $C_{21}H_{15}O_6N_3$ requires C, 62·2; H, 3·7%).

1-*Carbethoxy*-1-(3-m-*methoxyphenyl*-n-*propyl*)cyclo*pentan*-2-*one*.—3-*m*-Methoxyphenyl-*n*-propyl iodide (20 g.), prepared according to Robinson and Schlittler (*loc. cit.*), was added to ethyl potassio-*cyclo*pentan-2-onecarboxylate, prepared from powdered potassium (2·8 g.) and keto-ester (11·6 g.) in xylene (100 c.c.), and the mixture refluxed for 8 hours. The well washed and dried xylene solution was distilled, affording a colourless product (15 g., 70%), b. p. 165—170°/0·1 mm., $n_D^{17°}$ 1·5180. The *semicarbazone* separated from ethanol in colourless plates, m. p. 126° (Found: C, 63·5; H, 7·8. $C_{19}H_{27}O_4N_3$ requires C, 63·2; H, 7·5%).

1-(3-m-*Methoxyphenyl*-n-*propyl*)cyclo*pentan*-2-*one* (IX).—1-Carbethoxy-1-(3-*m*-methoxyphenyl-*n*-propyl)*cyclo*pentan-2-one (25·5 g.), barium hydroxide (80 g.), and water (150 c.c.) were refluxed for 12 hours. After cooling the mixture was acidified and allowed to stand overnight in order completely to decompose the barium salt. The acid, isolated by ether extraction followed by evaporation of the ether, was an uncrystallisable oil. It was mixed with powdered barium hydroxide (1 g.) and distilled slowly at atmospheric pressure. The distillate, in ether, was washed with alkali and water and dried, the ether evaporated, and the residue distilled, affording an oil (13·1 g.), b. p. 151—180°/0·4 mm., n_D^{15} 1·5307. The *semicarbazone* crystallised from ethanol in colourless feathery needles, m. p. 173° (Found: C, 66·3; H, 7·8. $C_{16}H_{23}O_2N_3$ requires C, 66·4; H, 8·0%).

The Action of Phosphoric Oxide on 1-(3-m-*Methoxyphenyl*-n-*propyl*)cyclo*pentan*-2-*one*.—The material was recovered unchanged after refluxing in toluene solution with additions of phosphoric oxide over a period of 3 hours. This recovered material (10·8 g.) in xylene (400 c.c.) was refluxed, with periodic additions of phosphoric oxide, for 50 hours. The sticky brown complex remaining after pouring off the xylene solution was treated with excess of alkali and extracted with ether. The combined ethereal extract and xylene solution were washed, dried, and distilled, affording a main fraction, b. p. 120—

123°/0·1 mm. This was redistilled, giving a colourless oil (3·5 g.), b. p. 104—107°/0·2 mm. (Found : C, 88·4; H, 11·4%). Distillation over sodium did not effect any change, b. p. 107—109°/0·2 mm., $n_D^{20°}$ 1·5042, $d_{20°}^{20°}$ 0·927, $[R]_D$ 66·40 [Found : C, 88·2; H, 11·3%; *M* (Rast), 208. $C_{14}H_{22}$ requires C, 88·3; H, 11·6%; $[R]_D$ (for 3 double bonds), 61·25; *M*, 190. $C_{15}H_{24}$ requires C, 88·2; H, 11·8%; $[R]_D$ (for 3 double bonds), 65·87; *M*, 204].

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223. *The Ternary System, Methanol–Methyl Acetate–Water.*

By A. G. CRAWFORD, G. EDWARDS, and D. S. LINDSAY.

The presence of a binary azeotrope of methanol and methyl acetate is confirmed. Its composition has been established as 33·2 mols. % of methanol, 66·8 mols. % of methyl acetate (previously reported as 35 mols. % of methanol). Vapour–liquid equilibrium diagram for the systems methanol–methyl acetate and methanol–methyl acetate–water are given.

A SOLVENT for organic materials, miscible in nearly all proportions with water, has lately been introduced. This consists of a mixture of methanol and methyl acetate. As the recovery of the solvent would customarily be carried out by distillation, a knowledge of the volatility relationships in the ternary mixture methanol–methyl acetate–water is desirable.

As a necessary preliminary to the elucidation of the equilibrium conditions a rapid method of estimation based on physical constants was evolved. It is customary to utilise the refractive index and specific gravity when suitable (York and Holms, *Ind. Eng. Chem.*, 1942, **34**, 345) because of the convenience of measurement, and these constants were chosen in this case. Determinations were conducted at 25°, and the results are shown in Table I. Fig. 1 is a ternary diagram of the lines of constant refractive index and specific gravity constructed from the results in Table I. The experimental results represent a point of estimation of refractive index

TABLE I.

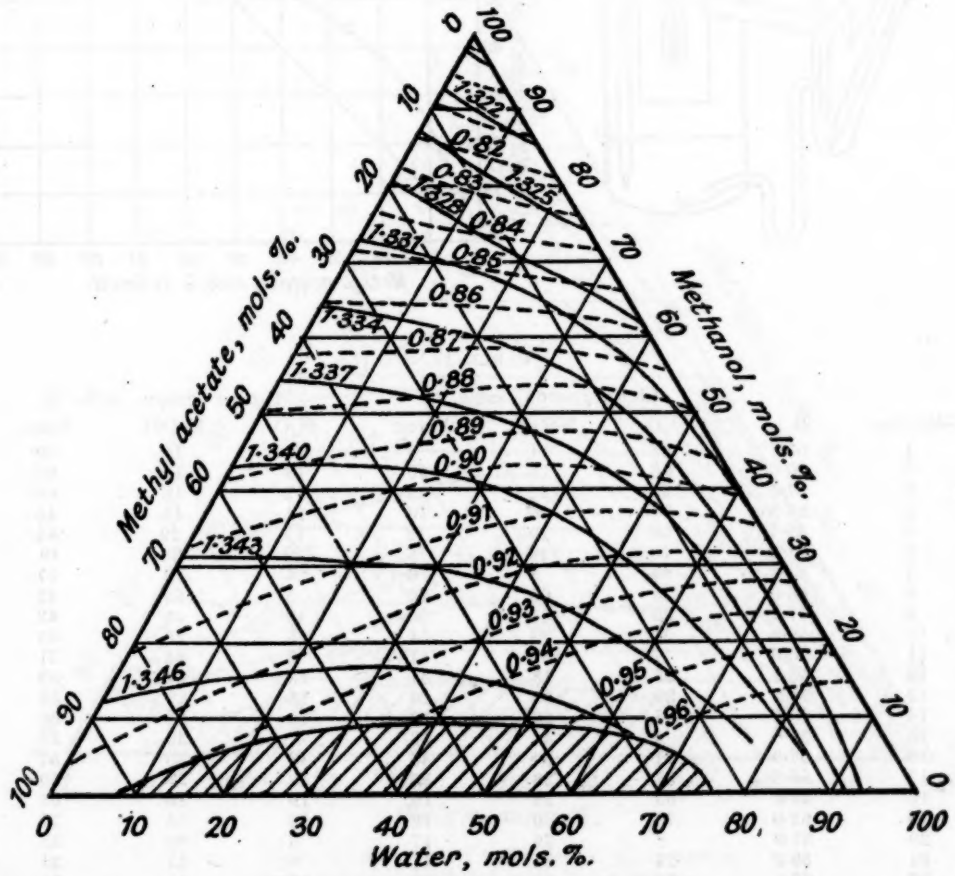
Soln. no.	Molar % (by wt.). MeOH.	Ester.	H_2O.	$n_D^{25°}$.	$d_{30°}^{25°}$.	Soln. no.	Molar % (by wt.). MeOH.	Ester.	H_2O.	n_D^{25}.	$d_{30°}^{25°}$.
1	10	80	10	1·34681	0·9243	32	20	20	60	1·34242	0·9428
2	20	70	10	1·34498	0·9143	33	30	10	60	1·33767	0·9259
3	30	60	10	1·34308	0·9061	34	10	20	70	1·34365	0·9636
4	40	50	10	1·34072	0·8953	35	20	10	70	1·33824	0·9460
5	50	40	10	1·33807	0·8823	36	10	10	80	1·33903	0·9726
6	60	30	10	1·33466	0·8674	37	90	10	0	1·32367	0·8132
7	70	20	10	1·33137	0·8500	38	80	20	0	1·32812	0·8343
8	80	10	10	1·32599	0·8275	39	70	30	0	1·33205	0·8524
9	10	70	20	1·34714	0·9287	40	60	40	0	1·33546	0·8667
10	20	60	20	1·34539	0·9202	41	50	50	0	1·33839	0·8811
11	30	50	20	1·34308	0·9098	42	40	60	0	1·34062	0·8929
12	40	40	20	1·34054	0·8977	43	30	70	0	1·34308	0·9033
13	50	30	20	1·33736	0·8832	44	20	80	0	1·34489	0·9129
14	60	20	20	1·33382	0·8686	45	10	90	0	1·34639	0·9196
15	70	10	20	1·32789	0·8496	46	90	0	10	1·32076	0·8044
16	10	60	30	1·34759	0·9394	47	80	0	20	1·32374	0·8225
17	20	50	30	1·34531	0·9214	48	70	0	30	1·32606	0·8425
18	30	40	30	1·34292	0·9133	49	60	0	40	1·32834	0·8612
19	40	30	30	1·34030	0·9028	50	50	0	50	1·33008	0·8817
20	50	20	30	1·33570	0·8842	51	40	0	60	1·33083	0·8950
21	60	10	30	1·33267	0·8656	52	30	0	70	1·33106	0·9253
22	10	50	40	1·34747	0·9413	53	20	0	80	1·32964	0·9459
23	20	40	40	1·34497	0·9307	54	10	0	90	1·32664	0·9674
24	30	30	40	1·34218	0·9185	55	0	90	10	immiscible	
25	40	20	40	1·33807	0·9034	56	0	80	20	,,	
26	50	10	40	1·33477	0·8863	57	0	70	30	,,	
27	10	40	50	1·34681	0·9469	58	0	60	40	,,	
28	20	30	50	1·34407	0·9367	59	0	50	50	,,	
29	30	20	50	1·34063	0·9223	60	0	40	60	,,	
30	40	10	50	1·33617	0·9058	61	0	30	70	,,	
31	10	30	60	1·34572	0·9564						

and specific gravity for all intersections of the composition lines on the ternary diagram (Fig. 1) except those along the base. No advantage would be gained, and considerable complexity

would be introduced, by plotting these as points on the diagram, and they have accordingly been omitted.

Because the refractive indices of methanol and methyl acetate differ by only 0·03011, it was essential to evaluate these to the fifth decimal place, and the Pulfrich refractometer was the only suitable instrument. Sufficient accuracy in the determination of specific gravity was obtained with Oswaldt–Sprengel picnometers (Daniels, Mathews, and Williams, " Experimental Physical Chemistry," McGraw Hill, 1934, p. 318) of 5 ml. capacity. For both refractive index and specific gravity estimations the temperature was controlled to $\pm 0{\cdot}1°$. This shaded area in Fig. 1 represents a region in which the solutions were not homogeneous. It will be appreciated that use of the experimental mixtures of Table I does not permit of accurate prediction of the

FIG. 1.



boundary of this area. Values for mutual solubility of water and methyl acetate at 25° are given (International Critical Tables, Vol. 3, p. 387; Hill and Morrow, private communication; Raymann, Diss., Budapest, 1906) as 0—24·1% of methyl acetate in water and 0—8·7% of water in methyl acetate. Owing to this immiscibility it was not possible to plot the physical constants in the region. The refractive index line 1·32299 to 1·33100 on the left of the apex of Fig. 1 should reappear in the lower right-hand corner of the graph and to the right of the tangential line 1·33100. Since these re-entrant curves all refer to solutions containing less than 4% of methyl acetate, and as determinations were only conducted for solutions differing in concentration by 10%, no attempt was made to indicate their position.

A number of stills have been suggested for the determination of vapour–liquid equilibria (York and Holms, *loc. cit.*; Baker, *Ind. Eng. Chem.*, 1943, **35**, 614; Jones, Schoenborn, and Colburn, *ibid.*, p. 666; Langdon and Keyes, *ibid.*, 1942, **34**, 938). The chief defect of these is the use of stopcocks, the lubrication of which is troublesome in presence of organic solvents. A

FIG. 2.

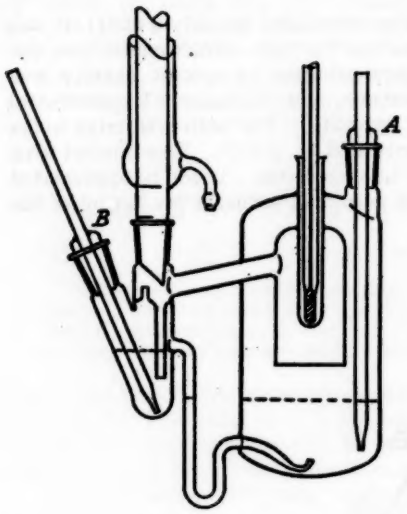


FIG. 3.

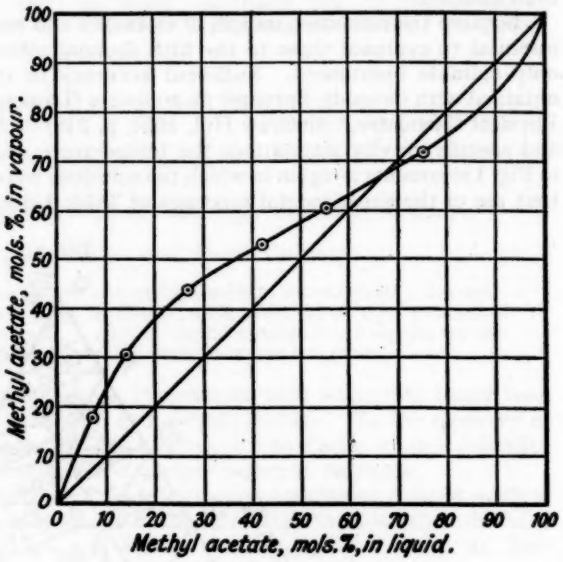
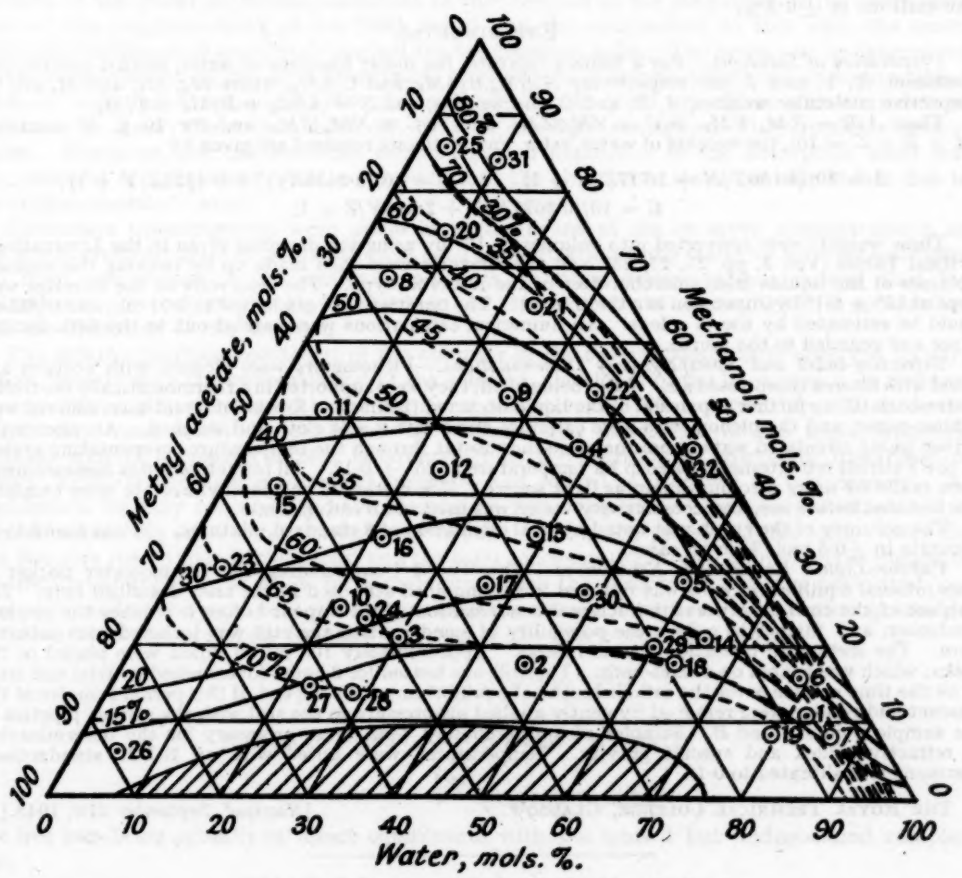


TABLE II.

Soln. no.	B. p.	Liquid compn., mols. %. H_2O.	MeOH.	Ester.	Vapour compn., mols. %. H_2O.	MeOH.	Ester.
1	63·7°	82	11	7	21	19	60
2	60·5	46	18	36	18	17	65
3	57·5	30	22	48	17	18	65
4	58·3	38	46	16	14	41	45
5	59·7	58	29	13	17	29	54
6	62·7	78	16	6	23	28	49
7	64·8	86	8	6	24	19	57
8	65·8	5	69	26	5	53	42
9	57·1	26	54	20	12	46	42
10	56·0	21	25	54	15	22	63
11	56·5	7	52	41	5	44	51
12	56·7	23	43	34	13	34	53
13	58·2	39	35	26	18	29	53
14	60·5	65	22	13	19	21	60
15	57·0	6	41	53	7	36	57
16	57·9	21	34	45	13	30	57
17	58·5	37	28	35	18	23	59
18	59·4	63	18	19	19	16	65
19	62·0	79	9	12	13	10	77
20	57·9	8	75	17	5	60	35
21	59·2	24	65	11	8	57	35
22	63·0	36	54	10	13	51	36
23	55·2	5	30	65	4	31	65
24	57·8	25	23	52	15	20	65
25	61·0	3	86	11	2	74	24
26	56·1	5	6	89	6	13	81
27	57·5	23	15	62	15	15	70
28	58·0	29	13	58	16	14	70
29	60·1	60	20	20	20	16	64
30	60·7	49	27	24	19	22	59
31	63·2	10	84	6	3	83	14
32	62·6	51	46	3	18	67	15
33	56·0	0	24	76	0	28	72
34	55·3	0	45	55	0	39	61
35	54·8	0	58	42	0	47	53
36	55·9	0	73	27	0	56	44
37	58·3	0	86	14	0	69	31
38	60·7	0	93	7	0	82	18

modification of the Othmer still in which stopcocks have been eliminated (Fig. 2) was used to evaluate the vapour–liquid relationships. To ascertain that equilibrium was in fact established in the modified equilibrium still, determinations were made with mixtures of methanol and water, the equilibrium relationships of which have been widely recognised (Doroszewsky and Polansky, *Z. physikal. Chem.*, 1910, **73**, 192; Uchida and Kato, *J. Soc. Chem. Ind. Japan*, 1934, **37**, 525; Cornell and Montonna, *Ind. Eng. Chem.*, 1933, **25**, 1331). Determinations of vapour composition over liquid methanol–water mixtures containing 6, 18, 42, 66, and 90 mols. % of methanol showed agreement with those of the above workers to within 1 mol. % in all cases.

FIG. 4.



— — — — — *Methyl acetate, mols. %, in vapour.*
——————— *Methanol, mols. %, in vapour.*

The numbers beside plotted points refer to Table II, which shows composition of the vapour at these points in the diagram.

Examination of the system methanol–methyl acetate confirmed the presence of a low-boiling binary azeotrope described by Ryland (*Amer. Chem. J.*, 1899, **22**, 384) and Holley (*J. Amer. Chem. Soc.*, 1902, **24**, 449). These workers reported an azeotrope containing 35 mols. % of methanol of b. p. 54·0°. The composition of the azeotrope now obtained was found in repeated physical and chemical tests to be 33·2 mols. % of methanol and 66·8 mols. % of methyl acetate. Its b. p. was 53·9°/760 mm. The complete equilibrium conditions are shown in Fig. 3.

No examination of the system methyl acetate–water was made because of the difficulties introduced by the low mutual solubility range.

The vapour–liquid equilibrium conditions for the ternary mixture were determined from a study of 32 mixtures. The results are shown in Table II. In Fig. 4, lines of constant concen-

tration of methyl acetate (broken lines) and of methanol (continuous lines) in the vapour over the liquid ternary mixtures have been plotted from the results of Table II. (The numbers beside plotted points refer to the vapour compositions given in the table.) It was found impossible to draw lines which would accurately represent the molecular concentration of water in the vapour phase. The lines representing concentrations of water in the vapour between 16 and 20 mols. % are exceptionally widely distributed over the graph so that an error of only 0·5% in its estimation results in a considerable displacement of the line. For this reason no attempt has been made to draw the water concentration lines. The mols. % of water in the vapour phase can be obtained by addition of corresponding percentages of methyl acetate and methanol obtained from Fig. 4 and subtraction from 100%. The accuracy of all ternary mixture estimations is $\pm 0{\cdot}5\%$.

Experimental.

Preparation of Solutions.—For a ternary mixture, the molar fractions of water, methyl acetate, and methanol, X, Y, and Z, are respectively A/SM_a, B/SM_b, and C/SM_c, where M_a, M_b, and M_c are the respective molecular weights, A, B, and C, the weights, and $S = A/M_a + B/M_b + C/M_c$.

Then $A/B = XM_a/YM_b$, $B/C = YM_b/ZM_c$, and $A/C = XM_a/ZM_c$, and for 10 g. of solution * ($A + B + C = 10$), the weights of water, ester, and methanol required are given by

$$A = 10/(4{\cdot}108Y/X + 1{\cdot}777Z/X + 1) \qquad B = 10/(0{\cdot}2434X/Y + 0{\cdot}4325Z/Y + 1)$$
$$C = 10/(0{\cdot}5627X/Z + 2{\cdot}312Y/Z + 1)$$

These weights were converted into volumes at 15° by using the densities given in the International Critical Tables (Vol. 3, pp. 25, 27, 28), and the mixtures were then made up by running the requisite volumes of the liquids from microburettes of the reservoir type. The reservoirs of the burettes were kept at 15° ± 0·1° by immersion in a thermostat. The burettes were graduated to 0·01 ml., and 0·002 ml. could be estimated by use of a lens. All numerical calculations were carried out to the fifth decimal place and rounded to the fourth.

Refractive-index and Specific-gravity Determinations.—Picnometers were cleaned with acetone and dried with filtered compressed air. After being filled, they were supported in a thermostatically controlled water-bath till no further expansion of the liquid occurred (2 hours). Excess of liquid was removed with a filter-paper, and the picnometers were carefully dried with a soft cloth and weighed. An electrically driven pump circulated water from the same thermostat through the temperature-compensating system of the Pulfrich refractometer to keep its temperature at 25° ± 0·1°. All refractive-index measurements were made by using a sodium lamp as light source. The methanol and methyl acetate were carefully fractionated before use, and conductivity water was used in all estimations.

The accuracy of the graph was tested by trial estimation of 8 standard mixtures. It was found to be accurate to ±0·5 mol. % in all cases.

Vapour–Liquid Equilibrium Estimations.—The "cowl" surrounding the thermometer pocket in conventional equilibrium stills was retained in the modified still used in the tests described here. The purpose of the cowl is to prevent fractional condensation of the vapour before it reaches the product condenser, and further to reduce the possibility of condensation the still was jacketed with asbestos fibre. The method of operation was as follows. Approximately 100 ml. of liquid were placed in the boiler, which was heated on a sand-bath. The still was heated for 3 hours (determined by trial and error to be the time necessary for the establishment of equilibrium). At the end of this period samples of the product and residue were removed by gently applied air pressure to the still with the sample pipettes in the sample points A and B. Samples of approximately 7 ml. were necessary for the determination of refractive index and specific gravity. Temperatures were noted with an N.P.L. standardised thermometer calibrated to 0·1°.

The Royal Technical College, Glasgow. [*Received, September 21st*, 1948.]

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224. *The Ionisation of Triphenylmethyl Bromide by Stannic Bromide.*

By Fred Fairbrother and Bernard Wright.

The ionisation of triphenylmethyl bromide by stannic bromide has been measured spectrophotographically in several solvents, and the equilibrium constants for the respective ionogenic and dissociation reactions calculated. The percentage ionisation in a given solvent varies linearly with the concentration of the solute, and varies with the solvent, from about 0·03% in very dilute benzene solution to about 8% in 5×10^{-3} M-ethyl bromide. Substitution of one bromine atom by a methyl radical destroys the ionising power in benzene solution.

In a previous communication (Fairbrother, *J.*, 1945, 503) the ionisation of the carbon–halogen bond in triphenylmethyl bromide by a catalytic inorganic halide was discussed, and a rough estimate of the extent of the ionisation by stannic bromide and by boron tribromide obtained from a study of the colour intensities of a few solutions of the respective complex compounds

* The size of the samples was restricted to 10 g. by the limited amount of pure ester available.

in benzene. An extended series of quantitative measurements of this ionisation by stannic bromide has now been made, and the equilibrium constants of the ionogenic and dissociation reactions :

$$(C_6H_5)_3CBr + SnBr_4 \rightleftharpoons [(C_6H_5)_3C^+ \cdot SnBr_5^-]^0 \rightleftharpoons (C_6H_5)_3C^+ + SnBr_5^-$$

determined in several solvents. The percentage of the triphenylmethyl bromide–stannic bromide complex which, on dissolution, is ionised, varies from about 0·03% in very dilute benzene solution to about 8% in 5×10^{-3} M-ethyl bromide solution : most of the remainder appears to revert to the original components.

In the present work the ionisation was determined by the measurement, in the several solvents, of the molar extinction coefficient of the complex at the maximum of the absorption band in the neighbourhood of $\nu = 2300$ mm.$^{-1}$ and the comparison of this with the molar extinction coefficient of completely ionised triphenylmethyl salts. The latter was re-determined by the measurement of the light absorption by solutions of triphenylcarbinol in concentrated sulphuric acid and a value of 35,000 obtained, which is in good agreement with the work of Anderson (*J. Amer. Chem. Soc.*, 1935, **57**, 1673) on the light absorption of the triphenylmethyl cation. Moreover, the characteristic double-humped maximum of the absorption band was also observed in the present work, confirming that the absorption measured was in fact due to the triphenylmethyl cation.

Extinction measurements were made in each solvent at six or seven concentrations, an average of seven separate determinations at each concentration being made for benzene solutions, and from one to four in the remaining solvents. Control determinations showed that the ionisation of pure triphenylmethyl bromide in the several solvents was negligible in comparison with the ionisation of the complex.

The molar extinction coefficient of the complex in the several solutions is observed to vary almost linearly with the concentration of the solution, the slopes of the lines, which do not pass through the origin, varying with the nature of the solvent. The relationship, shown in the figure, may most easily be explained as follows. The dissolution of the triphenylmethyl bromide–stannic bromide complex is equivalent to the addition of equimolar quantities of stannic bromide and triphenylmethyl bromide, and indeed is prepared in this manner. At equilibrium we may conceivably have in solution free components, components which are in dipolar association or as some non-ionically bound complex, ion pairs, and free ions. Only the last two give rise to the visible colour, and the total concentration of carbonium ions as measured spectrophotographically is made up of their sum, since the absorption bands of associated ions (ion pairs) and of the same ions when dissociated are usually so alike as to be indistinguishable.

If we write the equilibria formally in terms of the free components, then

$$\begin{array}{ccc} & \overset{k_1}{\rightleftharpoons} & [(C_6H_5)_3C^+ \cdot SnBr_5^-]^0 \\ (C_6H_5)_3CBr + SnBr_4 & \rightleftharpoons & (C_6H_5)_3C^+ + SnBr_5^- \\ & \underset{k_3}{\rightleftharpoons} & [(C_6H_5)_3CBr \cdot SnBr_4]^0 \end{array}$$

the free ions being actually in direct equilibrium with the ionised but undissociated complex, *viz.*,

$$[(C_6H_5)_3C^+ \cdot SnBr_5^-]^0 \underset{k'}{\rightleftharpoons} (C_6H_5)_3C^+ + SnBr_5^-$$

We cannot at present evaluate k_3, but the evidence indicates that it is small. If the non-ionic fraction of the solute remained substantially as a dipolar or co-ordinate complex rather than as free components, then the ionic fraction would vary in a manner different from that observed. The dielectric behaviour of the solutions in benzene is also against any massive formation of such a covalent complex (cf. Fairbrother, *loc. cit.*).

Let the total concentration of double compound dissolved be $[C]$, and the fraction present respectively as ionised but undissociated complex, as free ions, and as un-ionised complex, be α, β, and γ. Also, let the equilibrium constants as written be k_1, k_2, k_3, the numerical magnitudes of which are associated with the expression of all concentrations as molalities, then

$$k_1 = \alpha[C]/\{[C](1-\alpha-\beta-\gamma)\}^2 \text{ and } k_2 = (\beta[C])^2/\{[C](1-\alpha-\beta-\gamma)\}^2$$

Since the percentage of the solute which is ionised is in general small (0·3% in the most concentrated benzene solution, 3—4% in other solvents, and some 4—8% in ethyl bromide),

and, since the experimental variations inherent in the spectrophotographic method do not justify a more exact treatment, we can write :

$$k_1 \approx \alpha/[C] \text{ and } k_2 \approx \beta^2 \text{ for } (\alpha + \beta + \gamma) \ll 1$$

Moreover, since the molar extinction coefficient of the triphenylmethyl cation is 35,000 and the fraction of the solute which is ionised is $(\alpha + \beta)$, then the molar extinction coefficient of the solution is

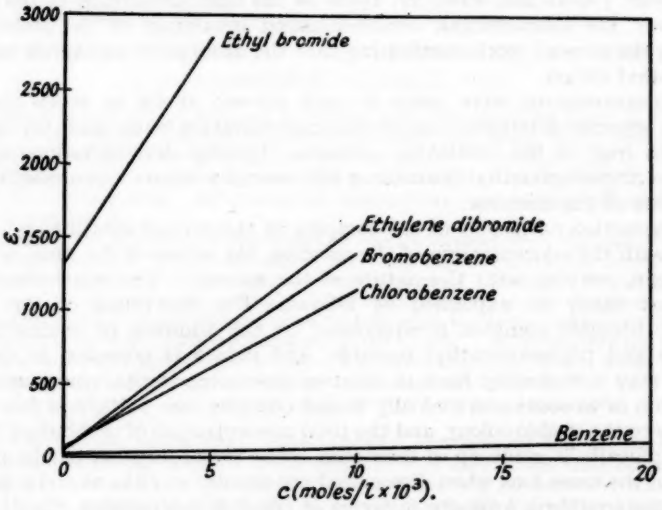
$$\varepsilon = 35{,}000 \times (\alpha + \beta)$$

and as

$$(\alpha + \beta) = k_1 C + \sqrt{k_2}$$

$$\varepsilon = 35{,}000 \times (k_1 C + \sqrt{k_2})$$

Hence, if the molar extinction coefficient is plotted against the molar concentration of the solution we should expect to obtain an approximately straight line with a slope of $35{,}000 \times k_1$ and an intercept at zero concentration of $35{,}000 \times \sqrt{k_2}$.



This does in fact obtain, as can be seen from the figure. These lines, calculated by the method of least squares from the experimental data, have the general form $y = a + bx$, in which for benzene $a = 8{\cdot}88$, $b = 5000$; for ethylene dibromide $a = 55$, $b = 152{,}000$; for bromobenzene $a = 53$, $b = 134{,}000$; for chlorobenzene $a = 78$, $b = 106{,}500$; and for ethyl bromide $a = 1320$, $b = 301{,}000$. Values of k_1 and k_2 calculated from these slopes and intercepts are given in the table, in which also are given $k' = k_2/k_1$, the dissociation constants of the ion pairs, the dielectric constants (D) of the solvents, and, for comparison, the fraction of the solute ionised in 5×10^{-3} M-solution (the highest concentration examined in ethyl bromide solution).

Solvent.	D.	k_1.	k_2.	k'.	Fraction ionised at 0·005M.
Benzene	2·28	0·14	$6{\cdot}4 \times 10^{-6}$	$4{\cdot}6 \times 10^{-7}$	0·0009
Ethylene dibromide	4·9	4·3	$2{\cdot}4 \times 10^{-4}$	$5{\cdot}6 \times 10^{-7}$	0·023
Bromobenzene	5·4	3·8	$2{\cdot}3 \times 10^{-4}$	$6{\cdot}1 \times 10^{-7}$	0·021
Chlorobenzene	5·9	3·0	$5{\cdot}0 \times 10^{-4}$	$1{\cdot}7 \times 10^{-6}$	0·017
Ethyl bromide	9·5	8·6	$1{\cdot}4 \times 10^{-3}$	$1{\cdot}6 \times 10^{-4}$	0·081

It must be concluded from the above considerations that even in benzene solutions a small fraction of the ions are free. It is possible that the existence of these free ions may contribute more to the abnormally high apparent molar dielectric polarisation of the ionic form, previously noted, than the presence of an un-ionised complex. The actual concentration of such free ions, however, is so small that, coupled with their large volume and therefore low mobility, the conductivities of the benzene solutions are too low to introduce any observable damping in the dielectric-constant measurements by the heterodyne method. A small conductivity in dry benzene solution, however, can be observed with a sensitive galvanometer.

It may be observed that both the total amount of ionisation and the fraction of this which is

present as free ions show a general increase with the dielectric constant of the solvent. The choice of solvent was restricted to those which did not interact with the stannic bromide.

A few experiments similar to those described above were carried out with mixtures of triphenylmethyl bromide and methyltribromotin in benzene solution. The results were sufficient to show that, at all events in benzene solution, little if any ionisation of the triphenylmethyl bromide occurs. Thus, the substitution of a methyl radical for a bromine atom in stannic bromide practically destroys the catalytic activity of the stannic compound. This result is to be attributed to a redistribution of electronic charge within the molecule, in the direction of a lessened ionic character of the Sn–Br bonds, an effect which is also manifested in the extension of carbon–halogen bond length when three of the halogen atoms in a stannic halide are successively replaced by methyl radicals (Skinner and Sutton, *Trans. Faraday Soc.*, 1944, **40**, 164).

Experimental.

Materials.—The triphenylmethyl bromide–stannic bromide double compound was prepared as before (Fairbrother, *loc. cit.*) by mixing equimolar quantities of the components, dissolved in sufficient warm benzene to prevent immediate precipitation, and allowing the solution to cool slowly. Solvents were purified and dried by methods appropriate to each.

Measurements.—The molar light-extinction coefficients were measured with the aid of a Hilger E2 quartz spectrograph, iron arc, and rotating-sector photometer, in the usual manner, with the following modifications. The photographic plates ordinarily used for ultra-violet spectrophotography proved to be inconveniently slow in the region of the absorption band of the triphenylmethyl cation, which is in the visible region of the spectrum, and we are indebted to Messrs. Ilford Ltd. for a specially cut supply of Ilford Press Ortho (Series II) which greatly speeded the determinations and minimised any change in the solutions during measurement. The location of the match points was greatly facilitated by printing positives on a glossy high-contrast contact paper. Pure solvent was used in the comparison cells except in measurements on mixtures of triphenylmethyl bromide and methyltribromotin, for which a solution of the tin compound was used for comparison in order to compensate for a slight colour instability of the latter. The cells varied in depth from 4 cm. for dilute benzene solutions to 1 mm. for the most concentrated ethyl bromide solutions. Measurements were made in a basement room of even temperature (*ca.* 15°): control measurements showed that effects of variation of temperature on the ionisation, far greater that those experienced, would not be detected.

We are indebted to the Anglo Iranian Oil Co, Ltd., for a grant to one of us (B. W.) during this work.

The University of Manchester. [*Received, September 25th*, 1948.]

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225. *Studies in the Azole Series. Part XI. The Interaction of α-Amino-nitriles, Hydrogen Sulphide, and Ketones.*

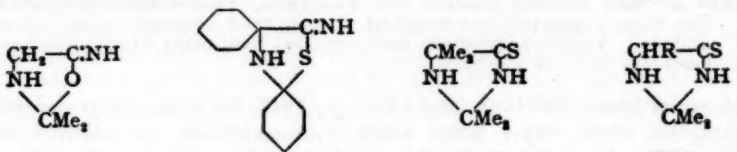
By A. H. Cook, Sir Ian Heilbron, and A. P. Mahadevan.

The interaction of aminoacetonitrile, acetone, and ethyl monothiobenzoate failed to give the expected 5-aminothiazole; instead, the monothio-ester appeared to provide the elements of hydrogen sulphide and the product was *4-mercapto-2 : 2-dimethyldihydroglyoxaline* (IV; R = H). The same compound was obtained directly from aminoacetonitrile, acetone, and hydrogen sulphide. Analogous products were obtained from other combinations of α-amino-nitriles and ketones but not aldehydes.

Part I of this series (Cook, Heilbron, and Levy, *J.*, 1947, 1594) described the ready formation of 5-aminothiazoles which takes place when α-amino-nitriles are allowed to react with dithio-acids or their esters. The present work had its inception in attempts to replace the dithio-ester by a monothio-ester. On allowing ethereal solutions of ethyl monothiobenzoate and aminoacetonitrile or α-aminobenzyl cyanide to stand at 0° for several hours no reaction was observed, although these were the conditions which sufficed to give 5-aminothiazoles from ethyl phenyldithioacetate. Attempts to effect the reaction at high temperatures were also abortive. In cases where the preparation of the thiazoles described earlier had proved somewhat difficult, the Schiff's bases of these compounds were obtained comparatively easily by allowing the amino-nitrile and dithio-ester components to react in presence of the appropriate ketones. Accordingly, aminoacetonitrile and the above monothio-ester were allowed to react in acetone solution containing a catalytic amount of pyridine, and on prolonged cooling a crystalline material, soluble in both alkali and dilute hydrochloric acid, separated from the reaction mixture. It appeared to give a solid hydrochloride on treatment with alcoholic hydrogen chloride, the base being regenerated from the salt by treatment with ammonium hydrogen carbonate; these observations were clearly at variance with its formulation as a Schiff's base. Moreover, though the compound gave a monoacetyl derivative, attempts to diazotise it proved unavailing.

Finally, analysis conclusively showed that the product was not related to the expected 5-aminothiazole, but seemed to indicate that it had been formed from acetone, hydrogen sulphide, and the amino-nitrile alone. The monothio-ester appeared merely to have contributed the elements of hydrogen sulphide, and it seemed worth while therefore to investigate the course of this reaction more closely. Accordingly, a study of the reaction was made with aminoacetonitrile and α-aminobenzyl cyanide on the one hand, and with acetone, methyl ethyl ketone, and acetophenone on the other. Ethereal solutions of the amino-nitriles were treated with an excess of the various ketones in presence of catalytic quantities of pyridine, and the mixtures then saturated with hydrogen sulphide. After several hours, the respective crystalline products separated in considerable yields. Of these, the compounds obtained from aminoacetonitrile and acetone, and from α-aminobenzyl cyanide and acetone, were selected for fuller study: the first product proved to be identical with the substance formed by use of ethyl monothiobenzoate, mentioned above. It had the composition $C_5H_{10}N_2S$, and the similar product from α-aminobenzyl cyanide had the formula $C_{11}H_{14}N_2S$. Both compounds were easily soluble in dilute acids and alkalis; the compound $C_{11}H_{14}N_2S$ yielded a *hydrochloride* from which it was regenerated by sodium hydrogen carbonate. The parent substances were further characterised as their *monoacetyl* derivatives. The latter were still soluble in dilute alkali without change and must be *N*-acetyl compounds. Pseudo-acidic groupings in these compounds were also evident from the formation of hydriodides of methyl derivatives on treating them with methyl iodide. Starting from α-aminobenzyl cyanide, the free methyl derivative was obtained from the salt on treatment with sodium hydrogen carbonate, and as it liberated methyl mercaptan on boiling with dilute sodium hydroxide, it must be an S-*methyl* derivative.

Acetone is known to condense with aminoacetonitrile in presence of a catalytic quantity of sodium methoxide to give a product which, as it affords aminoacetamide on treatment with water, has been formulated as (I) (Cook, Heilbron, and Levy, *J.*, 1948, 201). Bucherer and Brandt (*J. pr. Chem.*, 1934, **140**, 131) have obtained a product by heating *cyclo*hexanone cyanohydrin with ammonium sulphide which appears to be similar in behaviour to the new products under discussion. These authors observed that on dissolving the product in concentrated sulphuric acid and diluting the solution with water, a new material was obtained, evidently by replacement of an imino-group by oxygen, and for this reason they tentatively regarded it as (II). Gatewood and Johnson (*J. Amer. Chem. Soc.*, 1928, **50**, 1422) obtained a material of apparently similar nature by the action of hydrogen sulphide on α-amino*iso*butyronitrile and this they formulated, again tentatively, as (III). The experiments recounted in the present connexion leave little doubt that the compounds obtained by the action of hydrogen sulphide on amino-nitriles in the presence of ketones are to be formulated in the same manner. The representative compounds mentioned above are thus regarded as 4-*mercapto*-2 : 2-*dimethyl*- and -5-*phenyl*-2 : 2-*dimethyl-dihydroglyoxaline* (IV, or tautomerides; R = H and Ph, respectively).



(I.) (II.) (III.) (IV.)

If structure (IV) be accepted, it may well be that the cyclic compounds are preceded by the conversion of the α-amino-nitriles into α-amino-thioamides, and that the latter are the effective intermediates in the condensation with ketones. The thioamide of glycine could not be isolated after treating aminoacetonitrile with hydrogen sulphide (cf. Gatewood and Johnson, *loc. cit.*), but α-*aminophenylthioacetamide* was obtained from the corresponding nitrile by conducting the reaction in presence of a trace of pyridine, and was characterised as its *acetyl* derivative. This thioamide condensed spontaneously with acetone at room temperature to give (IV; R = Ph), identical with the material prepared earlier, and little doubt remains therefore of the course of the direct condensation between α-amino-nitriles, ketones, and hydrogen sulphide.

Experimental.

4-*Mercapto*-2 : 2-*dimethyldihydroglyoxaline*.—Aminoacetonitrile (11·2 g.) was suspended in ether (75 c.c.), and acetone (20 c.c.) added. After addition of a few drops of pyridine, hydrogen sulphide was passed in at 0° for 2 hours, and the solution kept at 5° for 12 hours. The solid (16·5 g.) which separated

was supplemented by a further crop (5·2 g.) obtained by evaporating the filtrate in a vacuum. The *thiol* crystallised from methanol as cubes, m. p. 154° (Found: C, 46·0; H, 7·8; N, 21·4. $C_5H_{10}N_2S$ requires C, 46·15; H, 7·7; N, 21·5%). It was soluble in ethanol, or hot water, and slightly soluble in ether or light petroleum. A solution of the substance in alcohol yielded on treatment with ethanolic hydrogen chloride, a crystalline hydrochloride which gave the parent compound on treatment with ammonium hydrogen carbonate. Recrystallisation from 95% ethanol converted it into what appeared to be *aminothioacetamide hydrochloride*, crystallising as glistening needles, m. p. 173° (decomp.) (Found: N, 22·0. $C_2H_7N_2ClS$ requires N, 22·1%). The compound also yielded a *picrate*, which crystallised from hot water as yellow needles, m. p. 143° (Found: N, 19·9; S, 8·9. $C_{11}H_{13}O_7N_5S$ requires N, 19·5; S, 8·9%).

The above compound (0·5 g.) was taken up in acetic anhydride (1 c.c.), and concentrated sulphuric acid (1 drop) added. Solution occurred, and the reaction was completed by a few minutes' heating under reflux. The solution was poured on ice, and the solid *acetyl* derivative recrystallised from toluene as beautiful leaflets, m. p. 204° (Found: C, 48·75; H, 6·8; S, 18·1. $C_7H_{12}ON_2S$ requires C, 48·8; H, 7·0; S, 18·6%).

The parent compound (0·5 g.) was dissolved in 2N-hydrochloric acid (10 c.c.). The solution was cooled in ice and treated slowly with stirring with a solution of sodium nitrite (0·5 g.) in water (1 c.c.). The solution became red and almost immediately a pale yellow precipitate appeared with vigorous effervescence. The reaction was completed by a few minutes' standing, and the precipitate (0·4 g.) crystallised on slow evaporation of its ethanol solution in very pale yellow needles. The *product* could be crystallised also from boiling water and then had m. p. 152° (decomp.) (Found: C, 37·8; H, 5·8; N, 21·6; S, 20·0. $C_{10}H_{18}O_3N_8S_2$ requires C, 37·4; H, 5·9; N, 21·8; S, 19·9%).

4-Mercapto-5-phenyl-2 : 2-dimethyldihydroglyoxaline.—α-Aminobenzyl cyanide (13·2 g.) in ether (120 c.c.) was treated with acetone (30 c.c.), and after addition of a few drops of pyridine, the solution was saturated with hydrogen sulphide for 2 hours while being kept at 0°. On allowing the mixture to stand at 5° for 48 hours, colourless prisms (17 g.) separated; these crystallised from 50% ethanol in colourless needles, m. p. 163° (Found: C, 64·1; H, 6·8; S, 15·5. $C_{11}H_{14}N_2S$ requires C, 63·9; H, 6·8; S, 15·2%). A solution of the *dihydroglyoxaline* in toluene yielded on treatment with ethanolic hydrogen chloride a *hydrochloride*, which recrystallised from ethanol as plates, m. p. 182° (Found: N, 11·6. $C_{12}H_{15}N_2ClS$ requires N, 11·6%). The picrate crystallised from hot water in reddish-yellow needles, m. p. 212° (darkening at 185°).

The above compound was taken up in acetic anhydride (2 c.c.), and concentrated sulphuric acid (1 drop) added. The clear solution was warmed to 90° for a few minutes and poured into ice-water; an oil separated which solidified on rubbing with ethanol. The *acetyl* derivative crystallised from ethyl acetate–light petroleum as colourless needles, m. p. 213—214° (Found: C, 62·8; H, 6·55. $C_{13}H_{16}ON_2S$ requires C, 62·9; H, 6·45%).

The above parent base (2 g.) was dissolved in concentrated hydrochloric acid (2 c.c.), diluted with water (15 c.c.), the solution cooled in ice, and treated with a solution of sodium nitrite (1 g.) in water (5 c.c.). There was immediate effervescence and a white solid separated. This was filtered off after the mixture had been kept in ice for 30 minutes, and the compound crystallised from toluene in needles, m. p. 157° (Found: C, 56·3; H, 4·9; N, 17·7%).

4-Mercapto-5-phenyl-2 : 2-dimethyldihydroglyoxaline (4 g.) was dissolved in ethanol (45 c.c.) and treated with excess of methyl iodide (2 c.c.). The solution was heated under reflux for 1 hour, cooled, diluted with light petroleum (100 c.c.), and kept at 5° for 24 hours. A glistening crystalline *hydriodide* (4 g.) was filtered off; it was easily soluble in water, and when recrystallised from ethanol–petroleum had m. p. 160° (decomp.) (Found: N, 7·7. $C_{12}H_{17}N_2IS$ requires N, 8·0%). Its aqueous solution was treated with excess of sodium hydrogen carbonate and kept at 0°. The solid was separated, and the mother-liquor extracted with ether. The combined ethereal extracts were evaporated to dryness in a vacuum, glistening plates (0·7 g.), m. p. 60°, being obtained. When recrystallised from a small quantity of ether (charcoal), *4-methylthio-5-phenyl-2 : 2-dimethyldihydroglyoxaline* had m. p. 61° (Found: C, 65·5; H, 7·3; N, 12·7. $C_{12}H_{16}N_2S$ requires C, 65·4; H, 7·2; N, 12·4%). It was soluble in dilute acid but not in alkali.

4-Mercapto-5-phenyl-2 : 2-dihydroglyoxaline (5 g.) was dissolved in 5% aqueous sodium hydroxide (50 c.c.), and the solution heated under reflux for 2½ hours, ammonia being evolved. The solution was filtered and neutralised, whereupon a white precipitate (*ca.* 1·5 g.) separated. Recrystallisation gave phenylglycine, m. p. 250° (indefinite), the identity of which was proved by its conversion into mandelic acid by the action of nitrous acid.

4-Mercapto-5-phenyl-2 : 2-dimethyldihydroglyoxaline (1 g.) was dissolved in 5% sodium hydroxide (4 c.c.). Excess of benzoyl chloride (*ca.* 0·6 c.c.) was added, and the mixture shaken thoroughly for a few minutes, the liquid being kept alkaline by addition of aqueous sodium hydroxide. An oil separated, and the reaction was completed by warming to 90° for a few minutes. The gritty *benzoyl* derivative recrystallised from aqueous ethanol in clusters of needles, m. p. 236—237° (Found: C, 69·9; H, 5·8; N, 8·9. $C_{19}H_{18}ON_2S$ requires C, 69·8; H, 5·8; N, 9·0%).

4-Mercapto-5-phenyl-2 : 2-dimethyldihydroglyoxaline (2 g.) was dissolved in aniline (5 c.c.), and the solution heated under reflux for 1 hour. The clear solution was poured into dilute hydrochloric acid at 0°, the supernatant liquid decanted, and the oil solidified. This was crystallised repeatedly from aqueous acetone, from which the *compound* crystallised as pale yellow needles, m. p. 178° (Found: C, 64·55; H, 5·8; N, 13·45. $C_{22}H_{22}N_4S_2$ requires C, 64·4; H, 6·3; N, 13·6%).

The following were also prepared by saturating a solution of the appropriate amino-nitrile and ketone in ether containing a few drops of pyridine as catalyst with hydrogen sulphide (all three were crystallised from aqueous ethanol): *4-Mercapto-2-methyl-2-ethyldihydroglyoxaline*, prisms, m. p. 147° (Found: C, 50·6; H, 8·4. $C_6H_{12}N_2S$ requires C, 50·6; H, 8·3%); the *2-phenyl-2-methyl* analogue, prisms, m. p. 157° (Found: C, 62·4; H, 6·7; N, 14·6. $C_{10}H_{12}N_2S$ requires C, 62·5; H, 6·25; N, 14·7%), and the *5-phenyl-2-methyl-2-ethyl* analogue, prisms, m. p. 135° (Found: C, 65·4; H, 7·45; N, 12·4. $C_{12}H_{16}N_2S$ requires C, 65·5; H, 7·3; N, 12·7%).

α-Aminophenylthioacetamide.—A solution of α-aminobenzyl cyanide (3·3 g.) in ether (25 c.c.) containing a few drops of pyridine was saturated at 0° with hydrogen sulphide for 1 hour. The solution was kept at 0° for 24 hours, large colourless prisms (0·5 g.) then having separated. These crystallised as plates, m. p. 98°, from ethyl acetate–light petroleum. The *amide* was easily soluble in all common organic solvents (Found: C, 57·9; H, 6·2. $C_8H_{10}N_2S$ requires C, 57·8; H, 6·0%). The corresponding *α-acetamido*-compound was prepared by shaking an aqueous suspension of the preceding compound with excess of acetic anhydride; on standing, large prisms separated, and these recrystallised from water as plates, m. p. 130° (Found: N, 13·4. $C_{10}H_{12}ON_2S$ requires N, 13·5%).

A solution of the α-aminophenylthioacetamide in ethyl acetate was treated with excess of acetone and allowed to stand in the cold for 12 hours. Colourless prisms separated which were identified with 5-mercapto-4-phenyl-2 : 2-dimethyldihydroglyoxaline obtained above.

4-Imino-5-phenyl-2 : 2-dimethyloxazolidine.—α-Aminobenzyl cyanide (2 g.) was dissolved in dry acetone (15 c.c.) and treated with a solution of sodium ethoxide in ethanol to give a permanent turbidity. The solution was kept at 5° for 12 hours, and the colourless prisms (1·5 g.) which separated were recrystallised from dry acetone; m. p. 144° (Found: C, 69·9; H, 7·4; N, 15·2. $C_{11}H_{14}ON_2$ requires C, 69·5; H, 7·4; N, 14·7%). The *oxazolidine* dissolved in warm water, but on boiling its solution it was converted into α-aminophenylacetamide. The parent compound failed to yield 4-mercapto-5-phenyl-2 : 2-dimethyldihydroglyoxaline on treatment with hydrogen sulphide.

Acknowledgment is made to the Rockefeller Foundation for assistance, and to the Government of Madras for a scholarship to one of us (A. P. M.).

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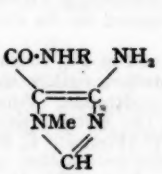
226. *Studies in the Azole Series. Part XII. Some Thiazolopyrimidines.*

By A. H. COOK, SIR IAN HEILBRON, S. F. MACDONALD, and A. P. MAHADEVAN.

5-Amino-4-carbethoxythiazoles (III) are readily converted into the corresponding thioureido-derivatives (V); the latter lose the elements of ethanol in cold dilute sodium hydroxide, passing into thiazolopyrimidines (VI) which are analogues of purines. Attempts to synthesise such compounds by attaching the thiazole to the pyrimidine ring were unsuccessful, one approach leading to the related ring system present in the thiazolopyrimidine (IX).

ONE of the prime objectives of the work described in this series has been, almost from its inception, the provision of simple and flexible methods of synthesising purines. The present memoir describes some experiments culminating in the preparation of thiazolopyrimidines which are skeletally similar to the purines. The following paper (Part XIII) records some further compounds of the thiazolopyrimidine group obtained by a somewhat different route, and a proof of the structures assigned by the conversion of one of the new compounds into a true purine of known structure. Finally, Part XIV generalises the method as one of wide applicability for the facile production of purines.

In recent years several syntheses of purines have been described in which the pyrimidine ring is affixed to an already existing iminazole group. Thus Sarasin and Wegmann (*Helv. Chim. Acta*, 1924, **7**, 713) used 4-amino-5-carbamyl-1-methylglyoxaline (I; R = H), completing the 6-membered ring by the use of ethyl carbonate, and Mann and Porter (*J.*, 1945, 751) used the related compounds (I; R = Me or Et) with ethyl chloroformate. The related synthesis of



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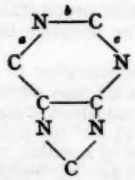

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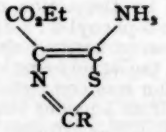
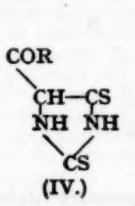


(III.)

purines by Allsebrook, Gulland, and Story (*J.*, 1942, 232) may be said to consist in effecting the bond *a* in the skeletal structure (II); those of Montequi (*Anal. Soc. Fís. Quím.*, 1927, **25**, 182) and of Baxter and Spring (*J.*, 1945, 232) in making the link *b*, and that of Mitter and Chatterjee (*J. Indian Chem. Soc.*, 1934, **11**, 867) in closing the bond *c*. None of these reactions appeared, however, to afford the desired flexibility and certain of them at least used intermediates which were the result of a series of tedious and sometimes drastic operations.

It was observed (Cook, Heilbron, and Levy, *J.*, 1947, 1598) that interaction of carbon disulphide and ethyl aminocyanoacetate yielded the thiazole (III; R = SH). In the present

work it has beeen shown that this compound could be easily converted into *4-carbethoxydithiohydantoin* (IV; R = OEt), and it was hoped that this by the action of ammonia might afford a 4(5)-amino-5(4)-carbethoxy- or -carbamyl-glyoxaline. The experiment, however, resulted only in the formation of *4-carbamyldithiohydantoin* (IV; R = NH_2) and it was therefore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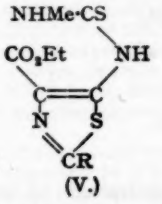
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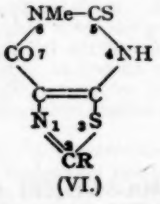
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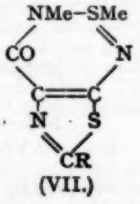
(VII.)

resolved, in view of the similarity between the glyoxaline and thiazole ring systems, to investigate the possibility in the first instance of fusing a pyrimidine ring to the thiazole ring of (III). Repeated attempts to make (III; R = SH) react with sodium cyanate in order to obtain the corresponding ureido-compound (cf. Allsebrook, Gulland, and Story, *loc. cit.*) were unavailing, but the related reaction with methyl *iso*thiocyanate proceeded readily to give *5-(N'-methylthioureido)-2-mercapto-4-carbethoxythiazole* (V; R = SH); this compound dissolved in cold dilute sodium hydroxide to give a yellow solution, and the product isolated on acidification after 2 hours' standing could on analytical evidence only be the thiazolopyrimidine (VI; R = SH) (the nomenclature and numbering follow " The Ring Index "). Methylation of this compound in alkaline solution with methyl sulphate afforded the *thiazolopyrimidine* (VII; R = SMe). The presence of the 2-methylthio-grouping was established by methylating (III; R = SH) to give 5-amino-2-methylthio-4-carbethoxythiazole (III; R = SMe) (Cook, Heilbron, and Levy, *J.*, 1947, 1598), which was characterised as its *acetyl* derivative and as the *azo-dye* obtained by coupling the diazotised product with β-naphthol. The parent amino-compound with methyl *iso*thiocyanate afforded the *thioureido*-derivative (V; R = SMe) and thence the *thiazolopyrimidine* (VI; R = SMe), first isolated as its sodium salt; methylation of this resulted in the formation of (VII; R = SMe), identical with the earlier preparation. Although the closure of the 6-membered ring in these and the following compounds is conveniently effected in cold alkaline solution, yet it also takes place with ease in other circumstances; thus (V; R = SMe) was cyclised to (VI; R = SMe) by heating with aqueous or alcoholic ammonia, or in boiling pyridine. Indeed, by carrying out the formation of (V; R = SMe) and analogous reactions for a prolonged period in hot pyridine, the pyrimidines could be isolated in a single stage.

With similar ease the thiazoles (III; R = H and CH_2Ph) were converted into the corresponding *N'-methylthioureido*-compounds (V; R = H and CH_2Ph) and thence into the *thiazolopyrimidines* (VI; R = H and CH_2Ph). These were methylated in alkaline solution to the corresponding *methyl* derivatives (VII; R = H and CH_2Ph). Earlier, attempts had been made to remove the mercapto-group in (III; R = SH) by means of chloroacetic acid in ethanol (cf. Foerster, *Ber.*, 1888, **21**, 1857) but the product was *5-amino-2-carbethoxymethylthio-4-carbethoxythiazole* (III; R = $S{\cdot}CH_2{\cdot}CO_2Et$) which was more conveniently prepared from (III; R = SH) by reaction with ethyl chloroacetate. This new thiazole also afforded a *N'-methylthioureido*-compound (V; R = $S{\cdot}CH_2{\cdot}CO_2Et$) and thence the *thiazolopyrimidine* (VI; R = $S{\cdot}CH_2{\cdot}CO_2H$), the acid obviously arising by simultaneous hydrolysis.

Although the pyrimidine nature of these products could hardly be doubted, further evidence was desirable. All gave a positive murexide reaction when oxidised by potassium chlorate in hydrochloric acid solution; oxidation products were obtained on treating (VI; R = SMe and H) with acid potassium chlorate and nitric acid, respectively, but their exact nature was not established. In these circumstances experiments were instituted to synthesise the thiazolopyrimidines by building the 5-membered on to a pre-formed 6-membered ring.

Condensation between *N*-methylthiourea and ethyl malonate afforded *2-thio-1-methylbarbituric acid* (VIII; R = H), which was converted by means of nitrous acid into the nitroso-derivative (VIII; R = NO) and thence into *5-amino-2-thio-1-methylbarbituric acid* (VIII; R = NH_2). All attempts, however, to make the last compound react with sodium dithioformate, or sodium or methyl dithiophenylacetate as a preliminary to attaching the 5-membered ring proved abortive, and steps were taken to circumvent this lack of reactivity. Ethyl thiophenylacetamidomalonate has been prepared by Todd and Topham (C.P.S. 93) from ethyl aminomalonate and methyl dithiophenylacetate. This compound has now been obtained from dithiophenylacetic acid, and a similar use of sodium dithioformate affords *ethyl*

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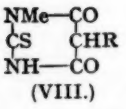
thioformamidomalonate. Condensation between *N*-methylthiourea and ethyl thiophenylacetamidomalonate gave an *isomeride* of (VI; R = CH_2Ph), which must be (IX) formed by ring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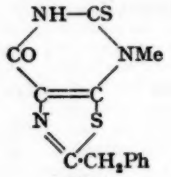
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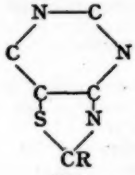
(X.)

closure of (VIII; R = NH·CS·CH_2Ph) in the undesired of the two possible directions. *N*-Methylation of (IX) and (VI; R = CH_2Ph) should formally lead to a common derivative, but experiments with the latter thiazolopyrimidine afforded only an *S*-methyl derivative (VII; R = CH_2Ph). In view, however, of the developments reported in the succeeding papers, the need for still another proof of the pyrimidine nature of the present compounds disappeared, and this part of the project was abandoned.

Thiazolopyrimidines have hitherto been almost unknown. Fischer and Ach (*Annalen*, **1895**, **288**, 167) prepared one having the same skeleton as the present compounds by boiling 4-thiouramil with acetic anhydride, and Weidel and Niemilowicz (*Monatsh.*, **1895**, **16**, 723) obtained the same by a modified procedure. More recently Erlenmeyer and Furger (*Helv. Chim. Acta*, **1943**, **26**, 366; **1947**, **30**, 585) have obtained thiazolopyrimidines with the related skeletal structure of (X) by the action of thioamides on 5-bromobarbituric acid.

Experimental.

5-Carbethoxy-2 : 4-dithiohydantoin (IV; R = OEt).—5-Amino-2-mercapto-4-carbethoxythiazole (8 g.), anhydrous sodium carbonate (8 g.), and absolute alcohol (40 c.c.) were heated together (sealed tube) at 100° for 18 hours. The solid was then filtered off and washed with ethanol, dissolved in water (150 c.c.) containing acetic acid (9 c.c.), and filtered (charcoal). From the solution the *dithiohydantoin* was precipitated by acidification with concentrated hydrochloric acid (20 c.c.); it was filtered off, washed with water (yield 6·4 g.), and crystallised from hot water as long yellow needles, m. p. 193° (Found : C, 35·6; H, 4·2; N, 13·2; S, 31·0. $C_6H_6O_2N_2S_2$ requires C, 35·3; H, 3·9; N, 13·7; S, 31·4%). This gave with acetic anhydride a *diacetyl* derivative crystallising from a mixture of ethyl acetate and petroleum as colourless needles, m. p. 113° (Found : C, 42·0; H, 4·1; S, 22·1. $C_{10}H_{12}O_4N_2S_2$ requires C, 41·7; H, 4·2; S, 22·2%). Desulphurisation of the compound with Raney nickel yielded 4-carbethoxyglyoxaline, identical with a sample prepared by the literature method.

5-Carbamyl-2 : 4-dithiohydantoin (IV; R = NH_2).—The above carbethoxydithiohydantoin (0·5 g.) was heated (sealed tube) with concentrated aqueous ammonia (3 c.c.) at 100° for 6 hours. The solution was evaporated to dryness in a vacuum, the gummy solid dissolved in hot water (5 c.c.), and the solution filtered (charcoal). Acidification with concentrated hydrochloric acid precipitated a yellow compound (0·4 g.), which crystallised slowly from hot water as plates, m. p. 242° (decomp.) (Found : C, 27·1; H, 3·1. $C_4H_3ON_3S_2$ requires C, 27·4; H, 2·9%).

5-Amino-2-methylthio-4-carbethoxythiazole (III; R = SMe).—5-Amino-2-mercapto-4-carbethoxythiazole (10·2 g.) was dissolved in 5% sodium hydroxide solution (150 c.c.). Methyl sulphate (8 c.c.) was added to the clear solution, and the mixture shaken for a few minutes. The solution warmed considerably and the curdy white solid (9·5 g.) which separated in a short time was filtered off and washed thoroughly with water. This crystallised from 50% ethanol as long flat needles, m. p. 108·5°, which gave with acetic anhydride in presence of a small amount of concentrated sulphuric acid an *acetyl* derivative, crystallising from 50% ethanol as colourless prisms, m. p. 82° (Found : C, 41·5; H, 4·65; N, 10·9. $C_9H_{12}O_3N_2S_2$ requires C, 41·5; H, 4·50; N, 10·8%). The parent amine (1 g.) was suspended in 5% hydrochloric acid (15 c.c.) and treated with sodium nitrite (0·5 g.) dissolved in a small amount of water. The clear red solution resulting in 15 minutes was dropped into an excess of a solution of β-naphthol in alkali maintained at 0°. The dark red precipitate was filtered off and washed with hot water. *2-Methylthio-4-carbethoxythiazole-5-azo-β-naphthol* crystallised from glacial acetic acid as glistening dark red needles, m. p. 167° (Found : C, 55·2; H, 4·2; N, 11·1. $C_{17}H_{14}O_3N_4S_2$ requires C, 54·7; H, 4·0; N, 11·3%).

5-(N'-Methylthioureido)-2-methylthio-4-carbethoxythiazole (V; R = SMe).—5-Amino-2-methylthio-4-carbethoxythiazole (11·0 g.) was dissolved in warm pyridine (30 c.c.), and an excess of methyl *iso*thiocyanate (6·0 g.) added. After being heated under reflux for 2 hours, the solution was poured on crushed ice (400 g.) and kept for 1 hour with occasional stirring. The yellowish-white solid (9·1 g.) which separated crystallised from aqueous ethanol as glistening needles, m. p. 157° (Found : C, 37·0; H, 4·7; N, 14·8. $C_9H_{13}O_2N_3S_3$ requires C, 37·1; H, 4·5; N, 14·4%).

7-Keto-5-thio-2-methylthio-6-methyl-4 : 5 : 6 : 7-tetrahydrothiazolo[5 : 4-d]*pyrimidine* (VI; R = SMe).—(*a*) *Sodium salt.* The above thioureido-compound (9 g.) suspended in ethanol (10 c.c.) was dissolved in warm 2% sodium hydroxide solution (200 c.c.). The yellow solution was filtered and kept overnight. White needles (5·4 g.) separated which, recrystallised from 90% ethanol, had m. p. 347° (decomp.).

(*b*) *Ammonium salt.* The thioureido-compound (2 g.) was suspended in concentrated aqueous

ammonia (30 c.c.) and heated in a sealed tube at 95° for 4 hours, whereupon most of the solid went into solution. On standing for 12 hours, glistening pale yellow needles (2 g.) had separated which recrystallised from very dilute aqueous ammonia as colourless needles, m. p. 270° (decomp.) (Found: C, 32·4; H, 4·1; N, 20·9. $C_7H_{10}ON_4S_3$ requires C, 32·1; H, 3·8; N, 21·4%). This *salt* was soluble in boiling water but tended to lose ammonia on continued boiling of the solution.

(*c*) *Free acid.* The mother-liquor after separation of the sodium salt in (*a*) was acidified with hydrochloric acid, whereby a greyish-white solid (2·2 g.) was obtained. A further quantity of the same compound was obtained by acidification of the mother-liquor after the precursor thioureido-compound had been filtered off. The free *acid* crystallised from glacial acetic acid, in which it was only very sparingly soluble, as colourless needles, or from nitrobenzene, as greyish micro-needles which had m. p. 265—266° (decomp.) (Found: N, 17·6; S, 39·6. $C_7H_7ON_3S_3$ requires N, 17·1; S, 39·2%). This was insoluble in water or ethanol and gave the murexide test when the oxidation was carried out with potassium chlorate and hydrochloric acid.

7-*Keto*-2 : 5-*dimethylthio*-6-*methyl*-6 : 7-*dihydrothiazolo*[5 : 4-d]*pyrimidine* (VII; R = SMe).—The above compound (1·0 g.) was dissolved in 2% sodium hydroxide solution (50 c.c.), and the solution shaken for a few minutes with methyl sulphate (1 c.c.). The white *pyrimidine* (1·0 g.) which soon separated crystallised from boiling ethanol as glistening felted needles, m. p. 218° (Found: C, 37·4; H, 3·8; N, 15·8; S, 36·9. $C_8H_9ON_3S_3$ requires C, 37·1; H, 3·7; N, 16·2; S, 37·1%).

5-(N′-*Methylthioureido*)-2-*mercapto*-4-*carbethoxythiazole* (V; R = SH).—5-Amino-2-thio-4-carbethoxythiazole (3·0 g.) was dissolved in warm pyridine (6 c.c.), and an excess of methyl *iso*thiocyanate (1·5 g.) added. The solution was heated under reflux in an atmosphere of nitrogen for 1 hour and poured on crushed ice (100 g.). The oil which separated solidified on standing, and the *thiol* (2·9 g.) was purified by dissolving it in acetic acid and precipitating it by addition of small amounts of water as micro-plates, m. p. 204° (Found: C, 35·2; H, 3·9; N, 15·0. $C_8H_{11}O_2N_3S_3$ requires C, 34·7; H, 4·0; N, 15·2%).

2-*Mercapto*-7-*keto*-5-*thio*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VI; R = SH).—A solution of the above thioureido-compound (1·0 g.) in 2% sodium hydroxide (25 c.c.) was kept for 2 hours and acidified, a grey solid (0·3 g.) being obtained. This could not be crystallised from the usual solvents, though it was slightly soluble in hot water, alcohol, and acetic acid. It was purified by dissolution in alkali and precipitation by hydrochloric acid, and obtained as a grey powder which did not melt below 350° (Found: N, 17·8. $C_6H_5ON_3S_3$ requires N, 18·1%). This *thiol* on methylation with methyl sulphate in alkali solution gave (VII; R = SMe), identical with that prepared from (III; R = SMe).

5-(N′-*Methylthioureido*)-4-*carbethoxythiazole* (V; R = H).—5-Amino-4-carbethoxythiazole (4·5 g.) in warm pyridine (12 c.c.) was heated under reflux with methyl *iso*thiocyanate (2 g.) for 2 hours, and the solution poured on crushed ice (200 g.). The pale yellow *thiazole* (3·2 g.) crystallised from 50% alcohol as plates, m. p. 180° (Found: C, 39·4; H, 4·9; N, 17·2; S, 26·4. $C_8H_{11}O_2N_3S_2$ requires C, 39·2; H, 4·5; N, 17·1; S, 26·1%).

7-*Keto*-5-*thio*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VI; R = H).—A solution of the above ureido-compound (2·7 g.) in 2% sodium hydroxide (50 c.c.) was kept for 2 hours and acidified without removal of the small amount of sodium salt which had separated as glistening white needles. The white *compound* (1·8 g.) so obtained crystallised from acetic acid in colourless needles, m. p. 295—300° (decomp.) (Found: N, 20·9; S, 32·7. $C_6H_5ON_3S_2$ requires N, 21·1; S, 32·2%).

7-*Keto*-5-*methylthio*-6-*methyl*-6 : 7-*dihydrothiazolo*[5 : 4-d]*pyrimidine* (VII; R = H). The preceding compound (1·0 g.) in 3% sodium hydroxide (40 c.c.) was methylated with methyl sulphate (1 c.c.). The white *methyl* derivative (0·9 g.) which separated crystallised from ethanol as needles, m. p. 207° (Found: C, 39·7; H, 3·5; N, 19·4; S, 29·9. $C_7H_7ON_3S_2$ requires C, 39·4; H, 3·3; N, 19·7; S, 30·0%).

7-*Keto*-5-*thio*-2-*benzyl*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d] *pyrimidine* (VI; R = CH_2Ph).—(*a*) *Sodium salt.* 5-Amino-4-carbethoxy-2-benzylthiazole (8·7 g.) was heated under reflux in pyridine (25 c.c.) with methyl *iso*thiocyanate (4 g.) and the solution was poured on crushed ice (400 g.). The solid was taken up in warm 2% sodium hydroxide (350 c.c.) and kept for 12 hours; long needles (2·9 g.) of the *sodium* salt had then separated. These crystallised from ethanol as white leaflets melting indefinitely above 300° (Found: N, 13·3; S, 20·6. $C_{13}H_{10}ON_3S_2Na$ requires N, 13·5; S, 20·6%).

(*b*) *Free acid.* The mother-liquor after separation of the sodium salt was acidified, whereupon a greyish-yellow solid (3·5 g.) separated. This *acid* crystallised from glacial acetic acid, in which it was very sparingly soluble, or from nitrobenzene as colourless plates, m. p. 285° (decomp.) (Found: C, 54·0; H, 3·4; N, 14·7. $C_{13}H_{11}ON_3S_2$ requires C, 54·0; H, 3·8; N, 14·5%).

7-*Keto*-5-*methylthio*-2-*benzyl*-6-*methyl*-6 : 7-*dihydrothiazolo*[5 : 4-d]*pyrimidine* (VII; R = CH_2Ph).—(*a*) The above compound (1·0 g.) was powdered and suspended in 5% sodium hydroxide (20 c.c.) and shaken with methyl sulphate (1 c.c.). The curdy white precipitate of the *methyl* compound (0·9 g.) was filtered off and crystallised from ethanol as greyish leaflets, m. p. 155° (Found: N, 13·6. $C_{14}H_{13}ON_3S_2$ requires N, 13·9%).

(*b*) The compound (1·0 g.) was treated with an ethereal solution (20 c.c.) of diazomethane (*ca.* 0·6 g.) (cf. Erlenmeyer and Furger, *Helv. Chim. Acta*, 1947, **30**, 585). There was immediate effervescence and a gummy solid separated. The reaction was completed by 4 hours' standing and removal of the solvent. The residue (0·75 g.) crystallised from aqueous ethanol as pale yellowish-grey needles, m. p. 155°, identical with those obtained by methylation with methyl sulphate.

(*c*) The compound (1·0 g.) was heated under reflux in ethanol (15 c.c.) with methyl iodide (0·5 c.c.) in presence of silver oxide (1·0 g.) for 3 hours. The dark solution was filtered and diluted with water, whereupon a turbidity appeared. Extraction with ether and evaporation of the ethereal extract gave a greyish-yellow solid (0·5 g.). This on repeated crystallisation from aqueous ethanol was found to be identical with the methylated product obtained by the preceding two methods.

5-*Amino*-2-*carbethoxymethylthio*-4-*carbethoxythiazole* (III; R = $S{\cdot}CH_2{\cdot}CO_2Et$).—5-Amino-2-mercapto-4-carbethoxythiazole (7 g.) and ethyl chloroacetate (5 g.) in ethanol (40 c.c.) were heated under reflux for 6 hours. The solution was diluted with warm water (100 c.c.) and cooled slowly. The solid *thiazole* (7·2 g.) recrystallised from light petroleum as colourless leaflets, m. p. 72° (Found: C, 41·4; H, 5·3;

N, 9·3; S, 21·6. $C_{10}H_{14}O_4N_2S_2$ requires C, 41·4; H, 4·8; N, 9·6; S, 22·1%). It was easily soluble in ethanol, ethyl acetate, or acetic acid. It gave an *acetyl* derivative on treatment with acetic anhydride, which crystallised from 30% ethanol in needles, m. p. 91° (Found: C, 43·7; H, 4·8. $C_{12}H_{16}O_5N_2S_2$ requires C, 43·7; H, 4·8%). The base could be diazotised in dilute hydrochloric acid and the diazonium salt coupled with β-naphthol to give a deep purple alkali-soluble dye.

The above compound (8·7 g.) in pyridine (15 c.c.) was refluxed with methyl *iso*thiocyanate (5 g.), the solution was added to crushed ice (300 g.), and the resulting solid crystallised from 50% ethanol (charcoal). 5-(N'-*Methylthioureido*)-2-*carbethoxymethylthio*-4-*carbethoxythiazole* (V; R = $S{\cdot}CH_2{\cdot}CO_2Et$) was obtained as slightly brown glistening needles (2 g.), m. p. 137° (Found: C, 39·8; H, 4·7; N, 11·5; S, 25·8. $C_{12}H_{17}O_4N_3S_3$ requires C, 39·8; H, 4·7; N, 11·5; S, 26·4%).

7-*Keto*-5-*thio*-2-*carboxymethylthio*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VI; R = $S{\cdot}CH_2{\cdot}CO_2H$).—The above thioureido-compound (1·5 g.) was dissolved in 5% sodium hydroxide (20 c.c.), and after 2 hours the solution was acidified, a yellowish-white solid (1·0 g.) being obtained. This *compound* crystallised from alcohol as glistening plates, m. p. 248° (decomp.) (Found: C, 33·9; H, 2·6; N, 14·0; S, 32·6. $C_8H_7O_3N_3S_3$ requires C, 33·8; H, 2·4; N, 14·5; S, 33·2%). It was sparingly soluble in hot ethanol but more readily soluble in hot acetic acid.

Oxidation of (VI; R = SMe) (cf. Fischer, *Ber.*, 1881, **14**, 1912; *Annalen*, 1882, **215**, 258).—To a suspension of the compound (1·0 g.) in 15% hydrochloric acid (30 c.c. was added in small amounts potassium chlorate (0·6 g.), the temperature being kept at 50—60°. After a further hour at 50° the solid *compound* (0·3 g.) was filtered off and crystallised from alcohol in glistening plates, m. p. 200°, sparingly soluble in hot water and soluble in alcoholic alkali (Found: N, 14·7. $C_5H_4O_4N_2S$ requires N, 14·7%).

Action of Nitric Acid on (VI; R = H).—To a suspension of (VI; R = H) (0·2 g.) in 35% nitric acid (4 c.c.) was added concentrated nitric acid (1 c.c.). In a few minutes a dark red solution was obtained and immediately a very pale yellow precipitate was formed. After dilution with water and separation, this solid (0·15 g.) crystallised with difficulty from glacial acetic acid–nitrobenzene as micro-needles, m. p. 243°.

2-*Thio*-1-*methylbarbituric acid* (VIII; R = H) (cf. Miller, Munch, Crossley, and Hartung, *J. Amer. Chem. Soc.*, 1936, **58**, 1090).—Sodium (9 g.) was dissolved in anhydrous ethanol (250 c.c.) and *N*-methylthiourea (17 g.) was added to the solution with stirring. Ethyl malonate (21 g.) was then quickly introduced, and the mixture heated under reflux for 7 hours. A very pale yellow solid separated, and after being kept for 12 hours at room temperature, the mixture was concentrated to a small volume (150 c.c.) and diluted with water (75 c.c.), a clear solution being obtained. This was made strongly acid with hydrochloric acid and cooled in ice. The *acid* (VIII; R = H) was obtained as a pale yellow solid (15·8 g.) which crystallised from boiling water as rods, m. p. 197° (Found: N, 17·5; S, 19·7. $C_5H_6O_2N_2S$ requires N, 17·7; S, 20·3%).

5-*Amino*-4 : 6-*diketo*-2-*thio*-1-*methylhexahydropyrimidine* (VIII; R = NH_2).—The above acid (15 g.), dissolved in 3% sodium hydroxide (200 c.c.), was treated with sodium nitrite (7 g.), and acetic acid (20 c.c.) added. After standing for 12 hours the dark liquid deposited a dark red precipitate; this was made into a paste with water (80 c.c.) and a solution of 16% ammonium sulphide (50 c.c.) was added. Heat was evolved and after standing for 1 hour the red solution was acidified and the precipitate filtered off. This was extracted with 10% sodium carbonate solution (3 × 20 c.c.) and the alkaline extract again acidified. The solid obtained (7 g.) was insoluble in all common solvents, turned pink on exposure to air and on boiling with solvents, and was purified by dissolution in alkali and reprecipitation by acid, then having m. p. 266° (decomp.) (Found: N, 23·8; S, 18·0. $C_5H_7O_2N_3S$ requires N, 24·3; S, 18·5%). All attempts to make this *amine* react with either sodium dithioformate or dithiophenylacetic acid proved unsuccessful.

Ethyl Thiophenylacetamidomalonate (cf. C.P.S. 93).—To ethyl aminomalonate (15 g.) was added an ethereal solution (150 c.c.) of dithiophenylacetic acid (15 g.), and the mixture kept at 5° for 24 hours. Hydrogen sulphide was evolved, and a white solid separated. After slow evaporation of the solvent, the residue was crystallised twice from light petroleum, white needles (12 g.), m. p. 74·5°, being obtained (C.P.S. 93 does not give a m. p. for this compound) (Found: C, 58·2; H, 6·5; N, 4·6; S, 10·7. Calc. for $C_{15}H_{19}O_4NS$: C, 58·3; H, 6·2; N, 4·5; S, 10·4%).

Ethyl Thioformamidomalonate.—To a solution of ethyl aminomalonate (10 g.) in ether (25 c.c.) was added a solution of sodium dithioformate (7·5 g.) in water (75 c.c.). The mixture was shaken for 3 hours and kept at 5° for 12 hours, a pale yellow crystalline solid separating. This *ester* recrystallised from light petroleum in long white needles (5 g.), m. p. 82° (Found: N, 6·1. $C_8H_{13}O_4NS$ requires N, 6·4%), easily soluble in alcohol, benzene, and ethyl acetate.

7-*Keto*-5-*thio*-2-*benzyl*-4-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (IX).—Sodium (7·4 g.) was dissolved in ethanol (120 c.c.) and *N*-methylthiourea (14·5 g.) was added. After addition of ethyl thiophenylacetamidomalonate (16 g.) the mixture was heated under reflux for 9 hours, a yellowish-white solid separating. This was brought into solution by addition of water (100 c.c.), and the solution acidified. On standing for 12 hours, a grey crystalline solid (4 g.) was obtained which recrystallised from acetic acid in plates, m. p. 214° (Found: N, 14·6. $C_{13}H_{11}ON_3S_2$ requires N, 14·5%). This *pyrimidine* was very sparingly soluble in ethanol and more soluble in boiling acetic acid.

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227. *Studies in the Azole Series. Part XIII. A Novel Synthesis of 9-Alkylpurines and Analogous Compounds.*

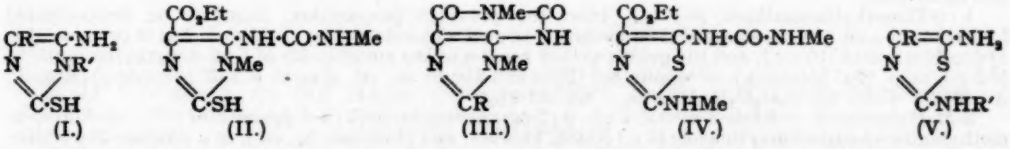
By A. H. Cook, J. D. Downer, and Sir Ian Heilbron.

A synthesis of 1 : 9-dimethyl*iso*xanthine is described starting from ethyl α-aminocyanoacetate and methyl *iso*thiocyanate. The preparation of some thiazolopyrimidines, *e.g.*, (VI) and (VIII), is also recorded.

The increasing interest shown in the polynucleosides has contributed to the evolution of several new syntheses of purines from glyoxalines (for references, see preceding paper. With the exception of that of Baxter and Spring (*J.*, 1947, 378), none of these syntheses has been employed in the building up of nucleosides owing to the fact that the appropriately orientated glyoxaline derivative is difficult of access.

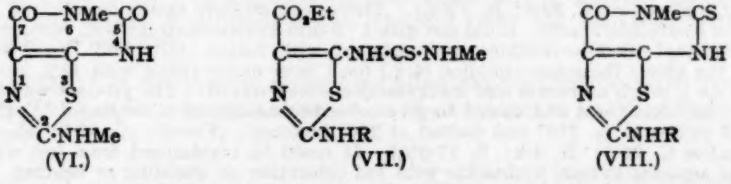
Earlier work in this series (Parts VI, VIII, and IX, *J.*, 1948, 1262, 1340, 2028) described the preparation of 2 : 5-diaminothiazole derivatives (I) from α-amino-nitriles and *iso*thiocyanates and their rearrangement under the influence of mild alkalis to give 5-acylamido-2-mercaptoglyoxalines where acyl *iso*thiocyanates had been employed, and 5-amino-2-mercapto-1-alkylglyoxalines (I; R′ = alkyl) where alkyl *iso*thiocyanates had been used. In the latter case it was appreciated that the isomerisation had afforded glyoxalines suitably oriented for the synthesis of 9-alkylpurines, it being remembered that C(9) is the location of the sugar residue in nucleosides of natural origin. Pursuing this approach, the present paper describes a purine synthesis employing 5-amino-2-mercapto-4-carbethoxy-1-methylglyoxaline (I; R = CO_2Et; R′ = Me) prepared as described in Part IX of this series.

Reaction of (I; R = CO_2Et; R′ = Me) with methyl *iso*cyanate gave 5-N′-*methylureido*-2-*mercapto*-4-*carbethoxy*-1-*methylglyoxaline* (II) which readily cyclised on treatment with dilute aqueous sodium hydroxide to the known 1 : 9-dimethyl-8-thiouric acid (III; R = SH) agreeing in both physical and chemical properties with those described for this purine in the literature (Biltz and Strufe, *Annalen*, 1921, **423**, 216) : its m. p., crystalline form and solubility were in complete agreement, and furthermore, on treatment with sodium nitrite it gave 1 : 9-dimethyl-*iso*xanthine (III; R = H), also identical with that prepared by Biltz and Strufe (*loc. cit.*). Finally, analysis and m. p. of the aurichloride of the synthetic compound (III; R = H) were compatible with the structure assigned.



The identification of the above product with 1 : 9-dimethyl-8-thiouric acid further confirms the structure of the glyoxalines prepared by rearrangement of 5-amino-2-alkylaminothiazoles (see Part IX).

This facile formation of the pyrimidine ring with dilute aqueous alkali was first employed by Cook, Heilbron, Mahadevan, and Macdonald (preceding paper) for the formation of thiazolopyrimidines. A number of related compounds have now been made from 2 : 5-diaminothiazole



derivatives by employing this facile cyclisation. Attempts to rearrange the thiazole ring at this stage to the respective purine proved abortive. Thus, on reaction of the thiazole (V; R = CO_2Et, R′ = Me) (see Part IX) with methyl *iso*cyanate, 2-*methylamino*-5-N′-*methylureido*-4-*carbethoxythiazole* (IV) was obtained, which readily cyclised in dilute aqueous alkali to 2-*methylamino*-5 : 7-*diketo*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VI), isomeric with 1 : 9-dimethylthiouric acid. Long heating, under reflux, of (VI) with 10% aqueous sodium

hydroxide gave two products, *viz.*, a *compound*, $C_6H_9O_2N_3S$, m. p. 226°, which appeared to possess pseudo-acidic properties and gave colour reactions for a thiol group, and a *compound*, m. p. 371°, isomeric with both (III; R = SH) and (VI). The latter compound was distinguished from the isomeride (VI) in that it dissolved in dilute aqueous hydrochloric acid; as it also gave a positive murexide test it may be 1 : 7-dimethyl-8-thiouric acid.

The *thiazolopyrimidines* (VIII; R = Me and CO_2Et) were made from the thiazoles (V; R = CO_2Et; R′ = Me and CO_2Et, respectively) by formation of the *methylthioureido*-derivatives (VII; R = Me and CO_2Et respectively) using methyl *iso*thiocyanate followed by cyclisation in alkali. It is of interest that the thioureido-compounds slowly cyclised when heated under reflux in pyridine, whereas (IV) did not do so under these conditions. The ease of formation of these thiazolopyrimidines is shown by the direct preparation of (VIII; R = Me) from ethyl α-aminocyanoacetate in one operation within a few minutes.

Experimental.

1 : 9-*Dimethylisoxanthine*.—5-Amino-2-mercapto-4-carbethoxy-1-methylglyoxaline (2·2 g.) (Cook, Downer, and Heilbron, *J.*, 1948, 1262), in pyridine (5 c.c.), and methyl *iso*cyanate (2 c.c.) were heated under reflux for 3 hours, methyl *iso*cyanate (1 c.c. portions) being added after the first and the second hour. The cold, clear, dark red solution was diluted with ethanol (5 c.c.) and ether (500 c.c.), and the crude precipitate purified from ethanol–ether to give light fawn needles (1·75 g.). Crystallisation from ethanol gave colourless, elongated, irregular prisms of *5-methylureido-2-mercapto-4-carbethoxy-1-methylglyoxaline* (II), m. p. 242° (decomp.) (Found: C, 42·1; H, 5·4; N, 22·0; S, 12·1. $C_9H_{14}O_3N_4S$ requires C, 41·8; H, 5·5; N, 21·7; S, 12·4%). It did not give a positive murexide test.

The preceding glyoxaline (1·4 g.), in 7·5% aqueous sodium hydroxide (15 c.c.), was boiled for 2 minutes, and the solution acidified with acetic acid. The crude product (0·7 g.), m. p. 371° (decomp.), was filtered off from the cold mixture and purified by repeated acid precipitation of its solution in dilute aqueous ammonia (100 vols.), to give almost colourless prismatic clusters of 1 : 9-dimethyl-8-thiouric acid (III; R = SH), m. p. 371° (decomp.) [Biltz and Strufe, *loc. cit.*, quote m. p. 370° (decomp.)] (Found: C, 39·3; H, 3·6; N, 26·2; S, 15·2. Calc. for $C_7H_8O_2N_4S$: C, 39·6; H, 3·8; N, 26·4; S, 15·1%). It gave a positive murexide test.

The above 1 : 9-dimethyl-8-thiouric acid (0·5 g.) was suspended in 6N-hydrochloric acid (2 c.c.), and powdered sodium nitrite (1·3 g.) added in small portions with stirring during 3 hours, according to the method described by Biltz and Strufe (*loc. cit.*). After this had stood overnight, water (5 c.c.) and concentrated hydrochloric acid (1·5 c.c.) were added, the whole warmed to effect solution, and the solution filtered. The filtrate was acidified with acetic acid, cooled, and filtered. The crude product (0·4 g.) was purified by repeated acid precipitation from its solution in dilute aqueous ammonia to give creamy needles of 1 : 9-dimethyl*isoxanthine* (0·3 g.), m. p. 350° (decomp.) [Biltz and Strufe, *loc. cit.*, quote m. p. 350° (decomp.)] (Found: N, 31·3. Calc. for $C_7H_8O_2N_4$: N, 31·1%). It gave a positive murexide test.

1 : 9-Dimethyl*isoxanthine* (0·1 g.), from the previous preparation, dissolved in concentrated hydrochloric acid (3 c.c.), was added to a solution of auric chloride (0·25 g., 0·12 mol. Au) in concentrated hydrochloric acid (10 c.c.), and the golden-yellow needles of the aurichloride of 1 : 9-dimethyl*isoxanthine* (0·2 g.), m. p. 254° (decomp.), were collected [Biltz and Strufe, *loc. cit.*, give m. p. 255° (decomp.)] (Found: Au, 37·9. Calc. for $C_7H_8O_2N_4,HAuCl_4$: Au, 37·9%).

2-*Methylamino-5 : 7-diketo-6-methyl-4 : 5 : 6 : 7-tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VI).—5-Amino-2-methylamino-4-carbethoxythiazole (4 g.) (Cook, Downer, and Heilbron, *loc. cit.*), in a mixture of pyridine (8 c.c.) and methyl *iso*cyanate (3 c.c.), was heated under reflux for 1 hour. The cold solution was diluted with ethanol (10 c.c.) and ether (300 c.c.) to give a cream-coloured solid (4·5 g.), m. p. 209° (decomp.). Crystallisation of the crude product from ethyl acetate (100 vols.) gave almost colourless prisms of *2-methylamino-5-N′-methylureido-4-carbethoxythiazole* (IV), m. p. 214° (decomp.) (Found: N, 21·5. $C_9H_{14}O_3N_4S$ requires N, 21·7%). It did not give a positive murexide test.

The preceding methylureidothiazole (1·3 g.) was boiled for 5 minutes in 5% aqueous sodium hydroxide (20 c.c.) and acidified while hot with acetic acid, giving a colourless solid (1 g.), m. p. 368—370°, which was purified by repeated precipitation from its solution in aqueous ammonia with acid, giving colourless, fine, isolated, hairy needles of the *thiazolopyrimidine*, m. p. 370—372° (decomp.) (Found: C, 39·7; H, 4·1. $C_7H_8O_2N_4S$ requires C, 39·6; H, 3·8%). This gave a positive murexide test, and was insoluble in dilute aqueous hydrochloric acid; it did not give 1 : 9-dimethyl*isoxanthine* with nitrous acid, nor did it yield 1 : 9-dimethyl-8-iodo*isoxanthine* on treatment with iodine (Biltz and Beck, *loc. cit.*).

On heating the above thiazolopyrimidine (4 g.) for 1 hour under reflux with 10% aqueous sodium hydroxide (120 c.c.), much ammonia and methylamine were evolved. The product was acidified with concentrated hydrochloric acid and cooled to give colourless needles of a *compound* (A) (2·2 g.), which became red and yellow at *ca.* 210° and melted at 226° (decomp.) (Found: C, 38·7; H, 4·9; S, 16·4. $C_6H_9O_2N_3S$ requires C, 38·5; H, 4·8; S, 17·0%). It could be crystallised from hot water and was soluble in dilute aqueous sodium hydroxide with red coloration on standing or heating. The filtrate from (*A*) was made alkaline with ammonia, filtered from impurities, acidified while hot with acetic acid, and filtered while still lukewarm to give colourless prisms (1 g.) of another *compound* (1 : 7-dimethyl-8-thiouric acid ?), m. p. 371° (decomp.) (Found: C, 39·9; H, 3·9; N, 26·2; S, 15·3. $C_7H_8O_2N_4S$ requires C, 39·6; H, 3·8; N, 26·4; S, 15·1%). It gave a positive murexide test, was soluble in dilute aqueous hydrochloric acid (cf. VI), but failed to give 8-iodo-1 : 9-dimethyl*isoxanthine* on treatment with iodine.

2-*Methylamino-7-keto-5-thiono-6-methyl-4 : 5 : 6 : 7-tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VIII; R = Me).—A mixture of 5-amino-2-methylamino-4-carbethoxythiazole (2 g.) and methyl *iso*thiocyanate

(0·7 c.c.), in pyridine (4 c.c.), was heated under reflux for 45 minutes, cooled, and filtered; the residual brownish solid (0·7 g.), m. p. 192° (decomp.) (a further 0·8 g. was obtained on keeping the filtrate overnight), on fractional crystallisation from pyridine (8 c.c.), gave colourless micro-needles (*B*) (0·2 g.), m. p. >360°, which were purified by extraction of the impurites with boiling alcohol (Soxhlet), and repeated acid precipitation from solution in dilute aqueous ammonia to give long, thin, hairy needles of the *thiazolopyrimidine*, decomposing above 325° but not melting below 360° (Found: C, 36·3; H, 4·0; N, 24·1; S, 28·5. $C_7H_8ON_4S_2$ requires C, 36·8; H, 3·6; N, 24·5; S, 28·1%). It gave a positive murexide test, and was insoluble in water and dilute acids, but soluble in aqueous alkalis. The pyridine filtrate from (*B*) was diluted with much water, and the resulting yellow solid (0·4 g.), m. p. 195°, crystallised from ethanol (15 c.c.) (charcoal) to give pale yellow, irregular, prismatic, silky needles of *2-methylamino-5-N′-methylthioureido-4-carbethoxythiazole* (VII; R = Me), m. p. 199° (decomp.) (Found: N, 20·7. $C_9H_{14}O_2N_4S$ requires N, 20·4%). It did not give a positive murexide test.

The above methylthioureido-thiazole (2·6 g.), on boiling for 4 minutes with 7·5% aqueous sodium hydroxide (45 c.c.), dilution with water (300 c.c.), and acidification at the boil with acetic acid, gave colourless needles of the derived thiazolopyrimidine.

The last-named thiazolopyrimidine was also obtained directly from ethyl α-aminocyanoacetate as follows: This ester (2·5 g.), methyl *iso*thiocyanate (4 c.c.), and pyridine (5 c.c.) in ether (22 c.c.) were heated on the steam-bath for 5 minutes, most of the ether then having evaporated. 7·5% Aqueous sodium hydroxide (30 c.c.) was added, the mixture brought to the boil, acidified whilst hot with acetic acid, and the thiazolopyrimidine filtered off and washed (1 g.), m. p. >360°.

2-Carbethoxyamino-7-keto-5-thiono-6-methyl-4 : 5 : 6 : 7-tetrahydrothiazolo[5 : 4-d]*pyrimidine* (VIII; R = CO_2Et).—5-Amino-2-carbethoxyamino-4-carbethoxythiazole (4 g.) (Capp, Cook, Downer, and Heilbron, *J.*, 1948, 2028) and methyl *iso*thiocyanate (1·2 c.c.) in pyridine (7 c.c.) were heated under reflux for 2 hours. The yellow solid (1·9 g.), sintering at *ca.* 190°, which separated on standing, was rubbed with ethanol (10 c.c.), and collected. Boiling the crude solid with methanol (30 c.c.) and filtering left the crude thiazolopyrimidine (0·05 g.), m. p. 290—300° (see below), which gave a positive murexide test. The methanol filtrate on concentration and dilution with ether gave a crude product (1·2 g.), which crystallised from ethanol–water (1 : 1; 50 c.c.) in pale yellow micro-crystals of *5-N′-methylthioureido-2-carbethoxyamino-4-carbethoxythiazole* (VII; R = CO_2Et), m. p. 199° (decomp.) (Found: C, 39·4; H, 4·9; N, 16·6; S, 18·8. $C_{11}H_{16}O_4N_4S$ requires C, 39·7; H, 4·9; N, 16·9; S, 19·3%). It did not give a positive murexide test.

The last-named methylthioureidothiazole (0·7 g.), when boiled for 5 minutes with 8% aqueous sodium hydroxide (30 c.c.), followed by acidification with acetic acid, cooling and filtration, gave a crude solid (0·65 g.), m. p. >360° (decomp.), which was purified by repeated acid precipitation of its solution in dilute aqueous ammonia to give pale cream micro-needles of the *thiazolopyrimidine* (Found: N, 19·4. $C_9H_{10}O_2N_4S_2$ requires N, 19·6%). It gave a positive murexide test.

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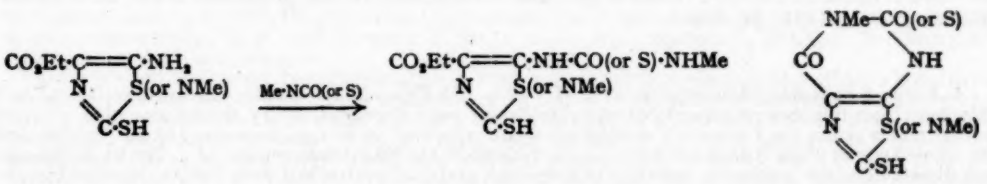
228. *Studies in the Azole Series. Part XIV. A New Synthesis of Purines.*

By A. H. COOK, A. C. DAVIS, SIR IAN HEILBRON, and G. H. THOMAS.

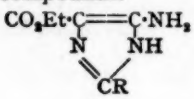
4-Aminoglyoxalines are generally accessible by condensing α-amino-nitriles with imino-ethers, thioimino-ether hydrochlorides, or formamidine hydrochloride. 4-Amino-5-carbethoxyglyoxalines (I) react with methyl *iso*thiocyanate or *iso*cyanate to yield 4-*N′*-methyl-thioureido- or -ureido-5-carbethoxyglyoxalines (IV; X = S or O, respectively) which are readily cyclised to 1-methyl-thioxanthines or -xanthines (III; X = S or O, respectively). These constitutions follow not only from analytical and other evidence, but also from the oxidation of typical compounds whereby the 5-membered dihydroglyoxaline ring is removed and a dimethylalloxantin and thence 3-methylalloxazine, identical with the materials prepared from theobromine, are obtained.

PARTS XII and XIII of the present series (preceding papers) demonstrated the facile fusion of a pyrimidine ring to an existing thiazole or, in one instance, to a glyoxaline structure in the following general manner:

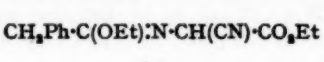


As one step in making this a generally useful procedure, it was first necessary to devise a general synthesis of 4-amino-5-carbethoxyglyoxalines (I). It had been recorded (Abraham, Baker, Barltrop, Chain, Waley, and Robinson, C.P.S. 549) that the reaction between ethyl aminocyanoacetate and phenacetiminoethyl ether could proceed in two ways: in the presence of one molecular proportion of hydrochloric acid the product was *N*-(α-cyano-α-carbethoxymethyl)phenacetiminoethyl ether (II), whereas interaction of the free bases afforded another base regarded as 4-amino-5-carbethoxy-2-benzylglyoxaline (I; R = CH_2Ph). With other iminoethers and ethyl aminocyanoacetate, always as free bases, this ring synthesis appears to be almost generally applicable, and *4-amino-5-carbethoxy-2-methyl-* and *-2-phenyl-glyoxaline* (I; R = Me and Ph, respectively) were formed at room temperature. With formimino-ethyl or *-iso*propyl ether reaction was unsatisfactory, but the required *4-amino-5-carbethoxyglyoxaline* (I; R = H) was obtained by replacing these iminoethers by formamidine hydrochloride. The reaction between α-aminonitriles and thioiminoethers proved, however, more satisfactory as a preparative method. The latter reactants could be used as their hydrochlorides in hot solvents, the glyoxaline hydrochlorides then being obtained directly in yields superior to those arising from *O*-iminoethers. In addition to the glyoxalines mentioned above, *4-amino-5-phenyl-2-benzyl-*, *-2-phenyl-*, and *-2-methyl-glyoxaline* were prepared in this manner from α-aminobenzyl cyanide.

The new glyoxalines were generally stable bases which could all be diazotised. Representative compounds were characterised as their *picrates*, *acetyl* derivatives, and *benzylideneamino*-compounds.



(I.)



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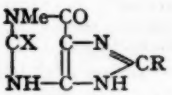

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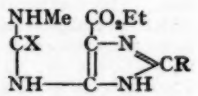

(IV.)

Previous syntheses of purines from glyoxalines were briefly reviewed in Part XII and the present work is concerned with the conversion of the 4-amino-5-carbethoxyglyoxalines described above into 1-methyl- and 1-methyl-2-thio-xanthines (III; X = O or S, respectively). 4-Amino-5-carbethoxy-2-benzylglyoxaline (I; R = CH_2Ph) reacted with methyl *iso*thiocyanate in boiling pyridine to give *4-N′-methylthioureido-5-carbethoxy-2-benzylglyoxaline* (IV; R = CH_2Ph, X = S). The latter behaved like the analogous compounds described in the preceding papers when dissolved in dilute sodium hydroxide, the *sodium* salt of *2-thio-8-benzyl-1-methylxanthine* (III; R = CH_2Ph, X = S) being formed, and the free purine being obtained on subsequent acidification. *4-N′-Methylthioureido-5-carbethoxyglyoxaline* and its *2-methyl* and *2-phenyl* derivatives (IV; R = H, Me, and Ph, respectively; X = S) were similarly prepared and cyclised to *2-thio-1-methyl-*, *-1 : 8-dimethyl-*, and *-8-phenyl-1-methyl-xanthine* (III; R = H, Me, and Ph, respectively; X = S).

In a similar fashion reaction of the appropriate 4-amino-5-carbethoxyglyoxaline with methyl *iso*cyanate afforded *4-N′-methylureido-5-carbethoxy-2-methyl-* and *-2-phenyl-glyoxaline* (IV; R = Me and Ph, respectively, X = O). These compounds cyclised in the same manner as the analogous thioureido-derivatives. By warming with dilute sodium hydroxide, *1 : 8-dimethyl-xanthine* and *8-phenyl-1-methyl-xanthine* (III; R = Me and Ph, respectively; X = O) were so prepared; the latter was also obtained by the desulphurisation of 2-thio-8-phenyl-1-methylxanthine with alkaline hydrogen peroxide.

The purine nature of these products could hardly be questioned, as all responded to the murexide test when oxidised with potassium chlorate in hydrochloric acid. It was, however, finally placed beyond doubt when 8-phenyl-1-methyl- and 1 : 8-dimethyl-xanthine were oxidised with potassium chlorate and the product reduced with stannous chloride to yield dimethylalloxantin identical with that prepared from theobromine (Biltz, *Ber.*, 1912, **45**, 3675). The identity was confirmed by its condensation with *o*-phenylenediamine to give the same 3-methylalloxazine as was obtained from authentic dimethylalloxantin prepared from theobromine (Kühling, *Ber.*, 1891, **24**, 3030).

Experimental.

4-Amino-5-carbethoxy-2-benzylglyoxaline (I; R = CH_2Ph).—Ethyl aminocyanoacetate (15 g.) and thiophenylacetiminobenzyl ether hydrochloride (30 g.) were dissolved in dry chloroform (200 c.c.) and heated under reflux for 1 hour. The solution was evaporated to 90 c.c., benzene (100 c.c.) added, and the whole kept at 0° for 3 days; the glyoxaline hydrochloride (20 g.) then separated. The hydrochloride was dissolved in the minimum quantity of hot water and just neutralised with 10% sodium hydroxide,

the free base (15 g.) being precipitated. The *picrate* crystallised from ethanol as rhombic prisms, m. p. 221° (decomp.) (Found : C, 48·4; H, 3·9; N, 17·8. $C_{19}H_{15}O_9N_6$ requires C, 48·1; H, 3·8; N, 17·7%).

4-Amino-5-carbethoxy-2-phenylglyoxaline (I; R = Ph).—(*a*) Benziminoethyl ether (15 g.) was added to ethyl aminocyanoacetate (17 g.; 1·3 moles) in ether (50 c.c.), and the solution kept at room temp. for 24 hours; the *glyoxaline* (1·75 g.) separated out. A further quantity (0·4 g.) was obtained on evaporating the solvent in a vacuum and keeping the residue at 0°. The glyoxaline was insoluble in water or ether and sparingly soluble in acetone or chloroform; it crystallised from ethanol as colourless prisms, m. p. 218° (decomp.) (Found : C, 61·9; H, 5·8; N, 18·0. $C_{13}H_{13}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%).

(*b*) Thiobenziminobenzyl ether hydrochloride (3 g.) and ethyl aminocyanoacetate (1·5 g.) were heated under reflux for 30 minutes in chloroform (25 c.c.); the *glyoxaline hydrochloride* (2·3 g.) which separated crystallised from methanol; m. p. 216° (decomp.) (Found : C, 53·5; H, 5·3. $C_{13}H_{14}O_2N_3Cl$ requires C, 53·8; H, 5·3%). The free base (1·1 g.) was precipitated from a hot aqueous solution of the hydrochloride (1·3 g.) by neutralisation with the minimum quantity of alkali. The *picrate*, prepared in ethanol, crystallised from this solvent as yellow needles, m. p. 224° (decomp.) (Found : C, 47·4; H, 3·6; N, 18·2. $C_{19}H_{16}O_9N_6$ requires C, 47·0; H, 3·5; N, 18·3%). Acetylation with acetic anhydride and concentrated sulphuric acid yielded a *monoacetyl* compound, which crystallised from water as colourless needles, m. p. 174° (Found : N, 15·8. $C_{14}H_{15}O_3N_3$ requires N, 15·4%). The *benzylidene-amino*-compound was prepared by dissolving the glyoxaline in hot benzaldehyde; it crystallised from ethanol as pale yellow microcrystalline needles, m. p. 214° (decomp.) (Found : N, 12·9. $C_{19}H_{17}O_2N_3$ requires N, 13·2%).

4-Amino-5-carbethoxy-2-methylglyoxaline (I; R = Me).—(*a*) Ethyl aminocyanoacetate (2·5 g.) and acetiminoethyl ether (2·9 g.) in ether (36 c.c.) deposited an oil on standing at room temperature for 24 hours; by treatment with ethanol and ether this yielded a small quantity of solid (0·1 g.), m. p. 167° (decomp.).

(*b*) Thioacetiminobenzyl ether hydrochloride (5 g.) was heated under reflux for 4 hours with excess of ethyl aminocyanoacetate (5 g.) in chloroform (30 c.c.); the *glyoxaline hydrochloride* (3·3 g.; 65%) which separated crystallised from a very small volume of ethanol as microscopic needles, m. p. 213—214° (decomp.) (Found : N, 20·6. $C_7H_{13}O_2N_3Cl$ requires N, 20·4%). The hydrochloride (2·8 g.) was converted into the free base (1·8 g.) in the usual manner, and the basified solution kept at 0° for 30 minutes to complete the precipitation. *4-Amino-5-carbethoxy-2-methylglyoxaline* was sparingly soluble in hot ether or benzene, more soluble in water, chloroform, or ethyl acetate, and readily soluble in ethanol; it crystallised from chloroform as colourless, granular, irregular prisms, m. p. 167° (decomp.) (Found : C, 49·4; H, 6·3; N, 25·1. $C_7H_{11}O_2N_3$ requires C, 49·7; H, 6·5; N, 24·9%). The m. p. of a mixture with the substance prepared from acetiminoethyl ether was undepressed.

4-Amino-5-carbethoxyglyoxaline (I; R = H).—To a solution of ethyl aminocyanoacetate (9 g.) in chloroform (200 c.c.) was added formamidine hydrochloride (5·6 g.) with just sufficient ethanol to dissolve it in the chloroform solution. On being heated under reflux for 2 hours, the solution darkened and was left for a further 12 hours at room temperature; the greater part of the ammonium chloride (2·8 g.; 80%) calculated for the reaction had then separated. Ether was added to the filtrate until a faint turbidity was obtained. On standing at 0° for 6 hours a very small quantity of black oil separated from which the solution was decanted, and on concentration by evaporation in a vacuum *4-amino-5-carbethoxyglyoxaline* (2·4 g.; 40%) crystallised out; this was readily soluble in alcohol and warm acetone, chloroform, or water, and crystallised from ethyl acetate–ethanol as colourless needles, m. p. 180—181° (Found : C, 46·4; H, 5·6; N, 26·6. $C_6H_9O_2N_3$ requires C, 46·4; H, 5·8; N, 27·1%).

4-Amino-5-phenyl-2-benzylglyoxaline.—Thiophenacetiminobenzyl ether hydrochloride (3 g.) was heated under reflux with α-aminobenzyl cyanide (1·7 g.) in chloroform for 12 hours, the glyoxaline hydrochloride gradually separating as a solid, m. p. 200° (decomp.). Precipitation of the solid (3 g.) was completed on standing at 0° for 12 hours. On dissolving this in the minimum quantity of water and just neutralising it with 10% sodium hydroxide, the *base* was precipitated (1·5 g.; 44%). It crystallised from pyridine or, better, methanol as leaflets, m. p. 199° (Found : C, 76·8; H, 6·0; N, 17·2. $C_{16}H_{15}N_3$ requires C, 77·1; H, 6·1; N, 16·9%). The *picrate* crystallised from ethanol as tufts of orange needles, m. p. 215° (Found : C, 55·3; H, 3·5; N, 17·3. $C_{22}H_{18}O_7N_6$ requires C, 55·2; H, 3·8; N, 17·6%). Acetylation with acetic anhydride and concentrated sulphuric acid at 100° yielded a *diacetyl* compound, which crystallised from methanol as colourless needles, m. p. 215° (Found : C, 71·8; H, 5·9; N, 12·3. $C_{20}H_{19}O_2N_3$ requires C, 72·0; H, 5·7; N, 12·6%).

4-Amino-2 : 5-diphenylglyoxaline.—Thiobenziminobenzyl ether hydrochloride (2 g.) and α-amino-benzyl cyanide (1 g.) were heated under reflux in chloroform for 2 hours, the glyoxaline hydrochloride (1·7 g.) being precipitated. The base was precipitated from a hot aqueous solution of the hydrochloride on neutralisation with sodium hydroxide as a white solid (1 g.) which rapidly turned green. The *picrate* formed silky needles, m. p. 220°, on crystallisation from ethanol (Found : C, 54·1; H, 3·5; N, 18·2. $C_{21}H_{14}O_7N_6$ requires C, 54·3; H, 3·5; N, 18·2%).

4-Amino-5-phenyl-2-methylglyoxaline.—Thioacetiminobenzyl ether hydrochloride (5 g.) and α-aminobenzyl cyanide (3·5 g.) were heated under reflux in chloroform (25 c.c.); an oil separated which, on cooling, solidified as colourless crystals (5 g.). The solid was very soluble in water or methanol and insoluble in acetone, and was not diazotisable in dilute hydrochloric acid. On rapid heating it melted at 125°; on continued heating gradual solidification occurred, followed by a second fusion at 225°. On 15 minutes' heating at 200°, the *glyoxaline hydrochloride* was obtained, which crystallised from methanol as colourless crystals, m. p. 238° (Found : N, 20·3. $C_{10}H_{11}N_3Cl$ requires N, 20·0%). It diazotised in dilute hydrochloric acid solution.

4-Amino-5-carbethoxy-2-benzylglyoxaline (1·2 g.) was added to a solution of methyl *iso*thiocyanate (0·4 g.) in pyridine (5 c.c.) and heated under reflux for 1 hour. On pouring into water (20 c.c.), a white solid (1·3 g.) was obtained which was sparingly soluble in ether or dilute hydrochloric acid, and soluble in ethanol, chloroform, or ethyl acetate. Long thin needles of *4-N'-methylthioureido-5-carbethoxy-2-benzylglyoxaline*, m. p. 174°, crystallised from ethanol (Found : C, 56·6; H, 5·9; N, 17·7; S, 10·1. $C_{15}H_{18}O_2N_4S$ requires C, 56·6; H, 5·7; N, 17·8; S, 10·1%). On dissolving this in 10% sodium

hydroxide, warming it for 1 minute, and acidifying the hot solution with acetic acid, *2-thio-8-benzyl-1-methylxanthine* was precipitated as a gelatinous solid (Found: C, 57·0; H, 4·4; N, 21·0; S. 12·2. $C_{13}H_{12}ON_4S$ requires C, 57·4; H, 4·4; N, 20·6; S, 11·8%).

4-Amino-5-carbethoxy-2-phenylglyoxaline (1·6 g.) and methyl *iso*thiocyanate (1 g.) were heated under reflux for 1 hour in pyridine (5 c.c.). On cooling at 0°, crystals of *4-N'-methylthioureido-5-carbethoxy-2-phenylglyoxaline* (1·3 g.) separated. A further quantity (0·7 g.) was obtained by pouring the mother-liquor into water (20 c.c.). The glyoxaline crystallised from ethanol in microprisms, m. p. 245° (Found: C, 55·1; H, 5·0. $C_{14}H_{16}O_2N_4S$ requires C, 55·3; H, 5·3%). On alkali treatment, followed by acidification, *2-thio-8-phenyl-1-methylxanthine* was obtained (Found: C, 55·8; H, 4·2; N, 21·5; S, 11·9. $C_{12}H_{10}ON_4S$ requires C, 55·8; H, 3·9; N, 21·7; S, 12·4%).

4-Amino-5-carbethoxy-2-phenylglyoxaline (5 g.) and a very large excess of methyl *iso*cyanate (15 g.) in pyridine (25 c.c.) were heated under reflux for 2 hours and then poured into water; *4-N'-methylureido-5-carbethoxy-2-phenylglyoxaline* (5·5 g.) was precipitated, and crystallised from ethanol as colourless prisms, m. p. 181—182° (Found: C, 58·2; H, 5·7; N, 19·1. $C_{14}H_{16}O_3N_4$ requires C, 58·3; H, 5·6; N, 19·4%). *8-Phenyl-1-methylxanthine* was obtained by alkali treatment followed by acid (Found: C, 59·9; H, 4·4; N, 23·1. $C_{12}H_{10}O_2N_4$ requires C, 59·5; H, 4·1; N, 23·1%). 2-Thio-8-phenyl-1-methylxanthine (1·5 g.) was dissolved in 5% sodium hydroxide (50 c.c.) to which was added at 0° hydrogen peroxide (20-vol., 13·5 c.c.). The solution was kept at 0° for one week. On boiling and acidifying with acetic acid, 8-phenyl-1-methylxanthine was precipitated (Found: C, 59·6; H, 4·2; N, 22·9%).

4-N'-Methylthioureido-5-carbethoxy-2-methylglyoxaline (1·8 g.) was obtained in the usual manner from 4-amino-5-carbethoxy-2-methylglyoxaline (2 g.) and methyl *iso*thiocyanate (1 g.). The compound was soluble in acetone, ethanol, or benzene and could be crystallised from ethyl acetate as colourless prisms, m. p. 194° (Found: C, 44·9; H, 5·8; N, 22·9. $C_9H_{14}O_2N_4S$ requires C, 44·6; H, 5·8; N, 23·1%). *2-Thio-1:8-dimethylxanthine* was precipitated on acidification of an alkaline solution of the ureido-compound (Found: C, 42·4; H, 4·1. $C_7H_8ON_4S$ requires C, 42·8; H, 4·1%).

4-Amino-5-carbethoxy-2-methylglyoxaline (3·1 g.) and a large excess of methyl *iso*cyanate (10 g.) in pyridine (10 c.c.) were heated under reflux for 2 hours. The pyridine was removed in a vacuum, and the residue boiled with 10% sodium hydroxide; acidification with acetic acid gave *1:8-dimethylxanthine* (2·2 g.; 67%), which separated as microcrystalline needles (Found: C, 47·1; H, 4·3; N, 31·3. $C_7H_8O_2N_4$ requires C, 46·7; H, 4·4; N, 31·1%).

4-Amino-5-carbethoxyglyoxaline (1·6 g.) and methyl *iso*thiocyanate (0·8 g.) in pyridine (5 c.c.) were heated under reflux for 1 hour and then poured into water; the thioureido-compound, m. p. 163° (2·0 g.), was precipitated. On dissolving this in alkali and acidification with acetic acid, *2-thio-1-methylxanthine* was obtained as small lustrous needles (Found: C, 39·7; H, 3·6; N, 30·4; S, 17·2. $C_6H_6ON_4S$ requires C, 39·6; H, 3·3; N, 30·8; S, 17·6%).

8-Phenyl-1-methylxanthine (2 g.) was suspended in a solution of concentrated hydrochloric acid (2·7 c.c.) and water (5 c.c.) at 60° and potassium chlorate (0·5 g.) was added during 30 minutes, care being taken to see that the temperature did not exceed 60°. The purine slowly dissolved, but towards the end of the experiment a solid started to crystallise and the deposition was completed by standing at 0° for 1 hour. The crystalline solid (0·6 g.) was filtered off, and air bubbled through the filtrate for 3 hours to remove excess of chlorine. Stannous chloride (1·3 g.) in concentrated hydrochloric acid (1 c.c.) was dripped into the solution, cooled to 0° to −5° in a carbon dioxide–ethanol bath, during 30 minutes. On standing at 0° for 12 hours, dimethylalloxantin (0·4 g.) separated, contaminated, probably, with some methyldialuric acid; it had m. p. 200° (to a red liquid) (Biltz, *Ber.*, 1912, **45**, 3675, gives m. p. 210—215°). A mixed m. p. with some dimethylalloxantin prepared from theobromine was undepressed. On boiling this with *o*-phenylenediamine hydrochloride in aqueous solution, 3-methylalloxazine was precipitated as a yellow-green solid which could be crystallised from acetic acid–ethanol (Found: C, 57·9; H, 3·3; N, 24·9. Calc. for $C_{11}H_8O_2N_4$: C, 57·9; H, 3·5; N, 24·6%). Both the 3-methylalloxazine prepared above and a specimen prepared from the theobromine decomposed at *ca.* 280° (Kühling, *Ber.*, 1891, **24**, 3030, gives decomp. 250°).

1:8-Dimethylxanthine (2 g.) was oxidised under identical conditions. Reduction of the oxidation product with stannous chloride yielded dimethylalloxantin (0·8 g.), which crystallised from water as colourless prisms, m. p. 207° (Found: C, 38·0; H, 3·3; N, 17·8. Calc. for $C_{10}H_{10}O_2N_4$: C, 38·2; H, 3·2; N, 17·6%).

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229. *Colchicine and Related Compounds. Part VII.*

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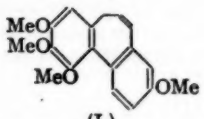
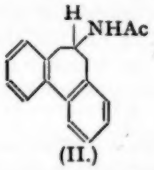
In connection with the interesting elimination of acetamide from *N*-acetylcolchinol methyl ether by means of phosphoric oxide, whereby the seven-membered ring compound deaminocolchinol methyl ether is obtained (Parts III and V), a study has been made of the action of phosphoric oxide on a series of acetylated amines having structural similarities to *N*-acetylcolchinol methyl ether. In most of these cases elimination of acetamide occurred, as with the colchicine derivative. The structure of *N*-acetylcolchinol methyl ether has not yet been completely established, and it may be that the conversion into deaminocolchinol methyl ether involves an enlargement of a six-membered ring. This possibility has been made much less probable by the synthesis of a *compound* having one of the structures (III) which has been under consideration for *N*-acetylcolchinol methyl ether. The synthetic compound (III), which has not

been resolved, was dehydrated by phosphoric oxide to give the *iso*quinoline derivative (VI). This behaviour is thus in sharp contrast to that of *N*-acetylcolchinol methyl ether.

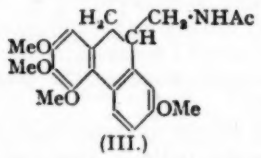
It was shown in Parts III and V (Cook and Graham, *J.*, 1944, 322: Barton, Cook, and Loudon, *J.*, 1945, 176) that *N*-acetylcolchinol methyl ether when heated with phosphoric oxide in xylene yields deaminocolchinol methyl ether (I) together with traces of the bond-isomeride, *iso*deaminocolchinol methyl ether. The process, which formally consists in the removal of acetamide, was subsequently used by Tarbell, Frank, and Fanta (*J. Amer. Chem. Soc.*, 1946, **68**, 502) for deaminating *N*-acetyliodocolchinol methyl ether, and by Cook, Dickson, and Loudon (Part VI, *J.*, 1947, 746; cf. Lettré, *Z. angew. Chem.*, 1947, **59**, 218) for converting (II) into the hydrocarbon corresponding to (I). Only in this last case is the structure of the parent amine definitely established, and further information on the deamination process has therefore been sought among suitable compounds of known structure. It was of particular interest to ascertain the behaviour of the acetylated amine (III) under the above treatment. The requisite material having been synthesised by an unambiguous route, the opportunity was taken to have the compound tested for the mitosis-arresting property, which characteristic of colchicine is retained in some degree by many degradation products of the alkaloid and appears to be adumbrated for amines of type (III) by the results reported in Part II (Cook and Engel, *J.*, 1940, 198).



(I.)

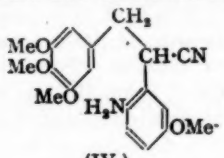


(II.)



(III.)

For the synthesis of (III), 3 : 4 : 5-trimethoxybenzyl chloride was condensed with *2-nitro-5-methoxybenzyl cyanide*, and the resulting *2-nitro-5-methoxy-α-(3′ : 4′ : 5′-trimethoxybenzyl)-benzyl cyanide* was reduced to the amine (IV). In a mildly alkaline medium and depending on the conditions used, the diazotised amine reacted to give one or other of two *compounds*, $C_{19}H_{19}O_4N_3$, which are probably derivatives of dihydrocinnoline and indazole respectively: they were not examined further. In an acid environment, however, the diazonium salt in



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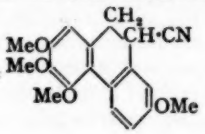
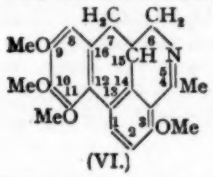


(V.)



(VI.)

presence of copper underwent a Pschorr type of cyclisation, affording *9-cyano-2 : 3 : 4 : 7-tetramethoxy-9 : 10-dihydrophenanthrene* (V). The structure of (V) was confirmed by hydrolysis to the corresponding *acid* followed by dehydrogenation of the methyl ester to the known ester of 2 : 3 : 4 : 7-tetramethoxyphenanthrene-9-carboxylic acid (Part IV; Buchanan, Cook, and Loudon, *J.*, 1944, 325). Hydrogenation of (V), using a platinum catalyst, and acetylation of the resulting base gave *2 : 3 : 4 : 7-tetramethoxy-9-acetamidomethyl-9 : 10-dihydrophenanthrene* (III).

When (III) was heated with phosphoric oxide in xylene, water was eliminated and the nitrogenous product is assigned the structure (VI). Accordingly it appears that the deamination reaction is here superseded by the usual Bischler–Napieralski synthesis of a dihydro*iso*quinoline from an acylated 2-phenylethylamine. The contrast thereby presented to the production of (I) from *N*-acetylcolchinol methyl ether strongly suggests that the latter compound cannot have a structure analogous to (III) and hence, by excluding the possibility of ring-enlargement during deamination, tends to confirm the view (Part V) that the 7-membered ring of (I) is already present in the amine, *viz.* colchinol methyl ether, itself. We are greatly indebted to Professor H. Lettré who has kindly examined the (±) compound (III) and reports that it shows a definite inhibitory effect on mitosis in chicken-heart fibroblasts, although it is considerably less potent than *N*-acetylcolchinol methyl ether.

The fact that (II) undergoes deamination rather than the Bischler–Napieralski reaction is probably due in part to the unfavourable steric conditions for the latter process, and, accordingly, in extending our inquiry to derivatives of diphenyl-ethylamine (VII) and -propylamine (VIII), search was made for basic products of the dihydro*iso*quinoline type. The requisite amines

(VII.) $CH_2Ph{\cdot}CH(NHR)Ph$ (VIII.) $CH_2Ph{\cdot}CH(NHR){\cdot}CH_2Ph$
(IX.) $CH_2Ph{\cdot}CH_2{\cdot}CH(NHAc)Ph$ (X.) p-$MeO{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}CH(NHAc)Ph$
(XI.) p-$MeO{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH{:}CHPh$ (XII.) p-$MeO{\cdot}C_6H_4{\cdot}CH{:}CH{\cdot}CH_2Ph$

were prepared by Leuckart's method (cf. Ingersoll *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 1808) from the appropriate ketones in reaction with formamide. The acetyl and benzoyl derivatives of 1 : 2-diphenylethylamine (VII; R = Ac or Bz) distilled unchanged, preferably under reduced pressure, although some stilbene was produced when the former was heated under reflux conditions (>300°). Both acyl derivatives readily afforded stilbene when heated with phosphoric oxide in xylene, and the absence of basic products showed that cyclodehydration to derivatives of 3 : 4-dihydro*iso*quinoline had not occurred. Even under the milder conditions used for the latter type of reaction by Gulland and Haworth (*J.*, 1928, 582), *viz.*, treatment with phosphorus pentachloride in cold chloroform, the benzoyl derivative gave some stilbene but no basic product. The *toluene*-p-*sulphonyl* derivative (VII; R = p-$Me{\cdot}C_6H_4{\cdot}SO_2$) could not be distilled without decomposition to stilbene, and it also afforded stilbene when heated with phosphoric oxide in xylene. In contrast to this behaviour the *toluene*-p-*sulphonyl* derivative (VIII; R = p-$Me{\cdot}C_6H_4{\cdot}SO_2$) of diphenyl*iso*propylamine was stable to distillation under reduced pressure and was recovered unchanged after being heated with phosphoric oxide in xylene. Diphenyl*iso*propylamine itself (VIII; R = H) was also unaffected by being heated with phosphoric oxide in xylene, but its *acetyl* derivative (VIII; R = Ac) afforded a mixture of 1 : 3-diphenylpropene and 3-*benzyl*-1-*methyl*-3 : 4-*dihydro*iso*quinoline* which was isolated as its *picrate*. 1-*Acetamido*-1 : 3-*diphenylpropane* (IX), similarly treated, yielded 1 : 3-diphenylpropene as the sole product isolated.

The results obtained with the acetylated diphenylpropylamines (VIII; R = Ac) and (IX) sufficiently indicate that the relevant derivatives of 1 : 3-diarylpropane may undergo the deamination reaction irrespective of whether the 1-(3) or 2-centre carries the amino-residue. In consequence, the fact of deamination is no guide to a more precise orientation of the amino-residue in *N*-acetylcolchinol methyl ether. Using the *compound* (X), an attempt was made to discover whether prototropic change to (XII) accompanied normal deamination to (XI) [cf. the simultaneous production of (I) with traces of its bond-isomeride], but, although (XI) was the only product identified, because of practical difficulties the possible formation of (XII) could not be definitely excluded and the point remains unsettled. The field of inquiry here covered is too restricted to permit of conclusions regarding the generality of the deamination process, and the results of a few experiments imply the need for caution. For instance, aceto*cyclo*hexylamide was smoothly converted into *cyclo*hexene and methyl cyanide, but neither acetoethylamide nor acetopropylamide yielded detectable quantities of the corresponding olefins.

Experimental.

2-Nitro-5-methoxytoluene.—This is conveniently prepared by the following method (cf. Buchanan, Loudon, and Robertson, *J.*, 1943, 168). Concentrated sulphuric acid (30 g.) was slowly added to 3-methoxytoluene (15 g.) at 30—40°, the solution being kept at that temperature until a test-portion gave no turbidity with water. Water (15 c.c.) was added, and then, with the temperature kept below 20°, nitric acid (15 c.c., d 1·42) was added with stirring. After 30 minutes the container was loosely covered (a vigorous reaction ensues) and was set aside for 12 hours without temperature control. The resulting mixture was diluted with water, and the solid product was collected, washed, dried, and purified by crystallisation or distillation; m. p. 55°, yield 60%.

2-Nitro-5-methoxybenzyl Cyanide.—2-Nitro-5-methoxyphenylpyruvic acid (37 g.) prepared as described by Blaikie and Perkin (*J.*, 1924, **125**, 296) but using potassium instead of sodium ethoxide, was dissolved in the minimum amount of warm ethanol, cooled rapidly, and poured into a cold solution of hydroxylamine in water (from 16·2 g. of hydroxylamine hydrochloride, 8·7 g. of sodium hydroxide, and 100 c.c. of water). The *oxime*, which separated on standing, had m. p. 170° (decomp.) from acetic acid (Found: C, 47·8; H, 3·8. $C_{10}H_{10}O_6N_2$ requires C, 47·25; H, 3·9%). It was dried and added portionwise to a fourfold weight of acetic anhydride at 100°. *2-Nitro-5-methoxybenzyl cyanide* was obtained by concentrating the solution under reduced pressure, and had m. p. 84° from benzene (yield 80%) (Found: C, 56·2; H, 4·3. $C_9H_8O_3N_2$ requires C, 56·2; H, 4·2%).

2-Nitro-5-methoxy-α-(3′ : 4′ : 5′-trimethoxybenzyl)benzyl Cyanide.—A solution of sodium ethoxide, made from sodium (0·66 g.) and ethanol (18 c.c.), was added to 2-nitro-5-methoxybenzyl cyanide (5 g.) dissolved in warm lime-dried ethanol (65 c.c.), and the resulting purple solution was treated with 3 : 4 : 5-trimethoxybenzyl chloride (5·56 g.) (Part III, *loc. cit.*), also in warm ethanol (40 c.c.). The whole, protected from moisture, was left at room temperature for 48 hours; the required product was then obtained as straw-coloured crystals, m. p. 163—164° from ethanol; yield 80% (Found: C, 61·4; H, 5·5; N, 7·5. $C_{19}H_{20}O_8N_2$ requires C, 61·3; H, 5·4; N, 7·5%).

2-Amino-5-methoxy-α-(3′ : 4′ : 5′-trimethoxybenzyl)benzyl Cyanide.—The above nitro-compound (8 g.), dissolved by gentle warming in sodium-dried dioxan (300 c.c.), was hydrogenated at ordinary temperature and pressure in presence of 2% palladised strontium carbonate (8 g.). Absorption was complete in

2 to 3 hours. The filtered catalyst was washed with warm dioxan, the combined filtrates were concentrated in a vacuum, and the residue was separated from some colloidal palladium by extraction with ether (charcoal). The recovered gummy amine was characterised as the *acetyl* derivative, m. p. 171—172° from ethanol (Found: C, 65·4; H, 6·4; N, 7·3. $C_{21}H_{24}O_5N_2$ requires C, 65·6; H, 6·25; N, 7·3%), but the crude amine was used for diazotisation.

9-Cyano-2 : 3 : 4 : 7-tetramethoxy-9 : 10-dihydrophenanthrene (V).—A solution of the above amine in dioxan (25 c.c.) was slowly poured into 3N-hydrochloric acid (72 c.c.) cooled in ice, and the resulting suspension was diazotised at −8° with sodium nitrite (1·28 g.) in water (20 c.c.), added during 15 minutes. After 1 hour's stirring, copper bronze (8 g.) was added (effervescence), and stirring was continued first (15 mins.) at −8° and then at room temperature (30 mins.). The product, which had begun to separate, was extracted with a little ether, and the two-layered mixture was left at 0° overnight. The copper was filtered off and extracted with warm ether, and the combined ether extracts were washed with brine and dilute sodium hydroxide and dried (K_2CO_3). The product, recovered from the ether, had m. p. 135—136° from methanol (Found: C, 70·3; H, 5·8; N, 4·5. $C_{19}H_{19}O_4N$ requires C, 70·15; H, 5·8; N, 4·3%), and the yield, based on the nitro-compound, was 45%.

Products $C_{19}H_{19}O_4N_3$.—(*a*) After diazotisation as before, the solution was made alkaline by addition of a slight excess of sodium carbonate, and was warmed gradually on the water-bath. After standing (at room temperature) overnight, the separated solid was collected, washed, dried, and crystallised several times from ethanol and finally from ligroin, forming almost colourless crystals, m. p. 122° (Found: C, 64·7; H, 5·55, N, 12·4. $C_{19}H_{19}O_4N_3$ requires C, 64·6; H, 5·4; N, 11·9%).

(*b*) The acid diazo-solution was poured into 10% sodium acetate solution, warmed to 50° and containing suspended copper bronze. After being heated to 70° the solution was left at room temperature overnight. An ether extract of the resulting solid was washed with dilute hydrochloric acid and then with water, and evaporated. The residue formed colourless crystals, m. p. 142° from ethanol (charcoal) (Found: C, 64·5; H, 5·2; N, 12·0%). A mixed m. p. of the products of (*a*) and (*b*) showed a marked depression.

2 : 3 : 4 : 7-Tetramethoxy-9 : 10-dihydrophenanthrene-9-carboxylic Acid.—The cyanide (V; 0·3 g.) was heated under reflux with potassium hydroxide (1 g.) in methanol (8 c.c.) for 48 hours. After concentration, addition of water, and extraction with ether, the aqueous layer was acidified; the precipitated *acid* had m. p. 190—192° from methanol (Found: C, 65·9; H, 5·7. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8%).

The acid (35 mg.) was esterified by the action of dry hydrogen chloride on a solution in methanol. After evaporation of the solvent over potassium hydroxide in a vacuum, the methyl ester, m. p. 121°, was recovered in ether and was dehydrogenated by heating it (20 mg.) with palladium black (10 mg.) at 200—230° for several hours in a slow stream of carbon dioxide. The apparatus was arranged so that any starting material which distilled unchanged was condensed on a further quantity of catalyst (10 mg.) and could then receive a second heat treatment. The product was distilled directly from the catalyst (245°/0·2 mm.), the condensate being identified by (micro) m. p. and mixed m. p. 99—102° (from methanol) as methyl 2 : 3 : 4 : 7-tetramethoxyphenanthrene-9-carboxylate.

2 : 3 : 4 : 7-Tetramethoxy-9-acetamidomethyl-9 : 10-dihydrophenanthrene (III).—The cyanide (V; 0·7 g.), dissolved in a mixture of acetic (30 c.c.) and sulphuric (1·2 c.c.) acids, was hydrogenated at ordinary pressure in presence of active Adams's catalyst (0·07 g.). Absorption was complete in several hours. The filtered solution was diluted with ether (250 c.c.) and then extracted with water (200 c.c. in all). The cooled aqueous extract was treated with a moderate excess of 15% aqueous sodium hydroxide and was then shaken with acetic anhydride (15 c.c.). The *acetamido*-compound separated on standing and formed micro-needles, m. p. 150° from ether; yield 66% (Found: C, 68·2; H, 6·6; N, 3·9. $C_{21}H_{25}O_5N$ requires C, 67·9; H, 6·7; N, 3·8%).

The amine *hydrochloride*, m. p. 226—228° (Found: C, 61·9; H, 6·6. $C_{19}H_{23}O_4N$,HCl requires C, 62·4; H, 6·6%), was similarly prepared by hydrogenating the cyanide (0·15 g.) in methanol (18 c.c.) to which had been added methanol (2 c.c.) saturated with hydrogen chloride. It was found advantageous to warm the flask occasionally during hydrogenation. The product was precipitated by adding ether to the concentrated filtrate.

Action of Phosphoric Oxide on (III).—The compound (III; 0·12 g.) was heated under reflux with phosphoric oxide (0·3 g.) in xylene (5·5 c.c.) for 30 minutes. The phosphoric residue, washed by decantation free of the solution which contained some unchanged (III), was treated with dilute sodium hydroxide. *3 : 9 : 10 : 11-Tetramethoxy-4-methyl-6 : 15-dihydro-5-azabenzanthrene* (VI), recovered in ether, formed yellow crystals, m. p. 156—157°, from ether (Found: C, 71·7; H, 6·5. $C_{21}H_{23}O_4N$ requires C, 71·4; H, 6·5%). It dissolved in hot dilute hydrochloric acid to a golden yellow solution from which, on cooling, slender orange needles of the hydrochloride crystallised, m. p. 218° (decomp.).

Amines of the diphenyl-ethylamine and -propylamine types were prepared by Leuckart's reaction from the appropriate ketone and formamide; the resulting formyl derivative was hydrolysed by heating it with hydrochloric acid, whereby the hydrochloride either crystallised or was isolated by passing dry hydrogen chloride through a dried solution of the base in ether.

Aceto-1 : 2-diphenylethylamide, m. p. 151° from ethanol (Leuckart and Janssen, *Ber.*, 1889, **22**, 1469, give m. p. 148°), distilled unchanged at 200° (air bath)/12 mm. or at 260—280° (air bath)/760 mm., but, after 30 minutes' heating at 325—340°, distillation of the residue gave stilbene, m. p. and mixed m. p. 121°, while the smell of acetamide was discernible. The amide (0·5 g.), phosphoric oxide (2 g.,) and xylene (35 c.c.) were heated under reflux for 20 minutes; the hot xylene solution was decanted, the phosphoric residue was washed with fresh hot solvent, and the combined solutions were fractionally distilled, affording stilbene (70%), b. p. 180—200° (air bath)/10 mm., m. p. and mixed m. p. 122°.

Benzo-1 : 2-diphenylethylamide, m. p. 176°, distilled unchanged at 310—325° (air bath)/755 mm. or 210—215°/10 mm., and gave a 60% yield of stilbene when treated as above with phosphoric oxide in xylene. The amide (1 g.) and phosphorus pentachloride (1·2 g.) in chloroform (7·5 c.c.) were kept for 3 days at room temperature. Aqueous extracts gave no basic material, but concentration of the dried chloroform solution afforded a semi-solid residue from which unchanged material, m. p. and mixed

m. p. 173—174°, was recovered by adding ligroin, while fractional distillation of the filtrate yielded stilbene, m. p. and mixed m. p. 120—122°.

Toluene-p-*sulphon*-1 : 2-*diphenylethylamide*, m. p. 104° from ethanol (Found : C, 72·1; H, 6·0. $C_{21}H_{21}O_2NS$ requires C, 71·8; H, 6·0%), when heated under distillation conditions yielded only stilbene, which was also obtained by concentrating the decanted solution after heating the sulphonamide with phosphoric oxide in xylene.

2-Amino-1 : 3-diphenylpropane yielded a hydrochloride, m. p. 198—200°, a picrate, m. p. 192° (cf. Rajagopalan, *Proc. Roy. Indian Acad. Sci.*, 1941, *A*, **14**, 127), an *acetyl* derivative, m. p. 105° from benzene–ligroin (Found : C, 80·7; H, 7·25. $C_{17}H_{19}ON$ requires C, 80·6; H, 7·5%), and a *toluene*-p-*sulphonyl* derivative, m. p. 99° from ethanol (Found : C, 72·4; H, 6·2. $C_{23}H_{23}O_2NS$ requires C, 72·3; H, 6·3%). Both acyl derivatives distilled under reduced pressure without decomposition, while the parent amine, recovered as hydrochloride (87%), and the sulphonamide (80% recovered) were unchanged by heating with phosphoric oxide in xylene.

The acetyl compound (0·5 g.) was heated under reflux for 30 minutes with phosphoric oxide (1 g.) in xylene (100 c.c.). Fractional distillation of the xylene layer gave 1 : 3-diphenylpropene (0·06 g.), b. p. 180° (air bath)/10 mm., which with bromine in carbon disulphide yielded the dibromide, m. p. 109°, identical with an authentic specimen prepared from phenylacetaldehyde (Stoermer and Thier, *Ber.*, 1925, **58**, 2611). The phosphoric residue was treated with 10% sodium hydroxide, and the basic portion when recovered in ether, dissolved in dilute hydrochloric acid, and treated with aqueous picric acid gave 3-*benzyl*-1-*methyl*-3 : 4-*dihydro*isoquinoline *picrate*, m. p. 149° from ethanol (Found : C, 59·5; H, 4·0. $C_{23}H_{20}O_7N_4$ requires C, 59·5; H, 4·3%).

1-Amino-1 : 3-diphenylpropane, isolated as the hydrochloride, m. p. 194°, formed a picrate, lemon-yellow plates, m. p. 183—185° (Found: C, 57·5; H, 4·3. Calc. for $C_{21}H_{20}O_7N_4$: C, 57·3; H, 4·5%) (Henrich, *Annalen*, 1907, **351**, 180, gives m. p. 155° for the picrate), and *N-acetyl* derivative, colourless needles, m. p. 76—77° from benzene–ligroin (Found : C, 80·8; H, 7·5. $C_{17}H_{19}ON$ requires C, 80·6; H, 7·5%).

The *N*-acetyl compound (0·5 g.) was treated with phosphoric oxide (2 g.) in xylene (20 c.c.); the residue obtained from the xylene concentrates yielded 1 : 3-diphenylpropene (0·35 g.), b. p. 140—160° (air bath)/1 mm., which was identified by conversion into the dibromide, m. p. and mixed m. p. 108—110°.

1-*Acetamido*-1-*phenyl*-3-(p-*methoxyphenyl*)*propane* (X), m. p. 117° from aqueous ethanol, was prepared by shaking an aqueous solution of the crude hydrochloride (m. p. 156°) of the base with acetic anhydride and alkali (Found : C, 76·2; H, 7·4. $C_{18}H_{21}O_2N$ requires C, 76·4; H, 7·4%). The acetyl (3·8 g.) was heated for 30 minutes with phosphoric oxide (7 g.) in dry xylene (30 c.c.). The xylene solution yielded a volatile product (1·3 g.), b. p. 206—208°/12 mm., and a large amount of non-volatile resin. The volatile product, when titrated with a standard solution of bromine in chloroform, showed the expected titre for a phenylmethoxyphenylpropene, but the last drops of the titration produced a dark green colouration [which was not observed with an authentic sample of (XI) prepared as described by Ingold and Shoppee (*J.*, 1929, 447)]. The gum, obtained from the concentrated chloroform solution, was dissolved in benzene and passed through a short column of alumina which removed most of the colour. The recovered gum was dissolved in warm petroleum (b. p. 60—80°) from which a solid fraction slowly separated, m. p. 87—90°, raised to 94° from methanol, and undepressed by admixture with 2 : 3-dibromo-1-phenyl-3-*p*-methoxyphenylpropane of m. p. 94°. Attempts to obtain crystalline material from the gum remaining in the mother-liquor were unsuccessful.

Aceto*cyclo*hexylamide (12 g.) in dry xylene (35 c.c.) was gently heated with phosphoric oxide (10 g.) under distillation conditions. At 90° (bath temp.) the phosphoric oxide darkened, and a low-boiling fraction began to distil and came over steadily while the temperature was kept at 135° (*i.e.*, below the b. p. of the xylene) for 1 hour (fraction *A*). Thereafter the temperature was raised, and half of the liquid remaining in the flask was distilled (fraction *B*). Fraction *A* was separated into a water-soluble (*C*) and a water-insoluble (*D*) fraction by washing it with water (3 × 10 c.c.). Fraction *C*, recovered from the water by saturating the solution with potassium carbonate, had b. p. 79°/755 mm. and was identified as methyl cyanide (1·35 g., 39%) by reduction with sodium in ethanol to ethylamine, from which the picrate, m. p. and mixed m. p. 168—170°, and 2 : 4-dinitrophenyl derivative, m. p. and mixed m. p. 113—114°, were prepared. Fraction *D* distilled at 81°/760 mm. and had the characteristic smell of *cyclo*hexene (1·36 g.; 19%) : it was unsaturated to bromine, and a portion, oxidised with potassium permanganate, gave adipic acid, m. p. and mixed m. p. 151—152°. Fraction *B* (controls having shown that the procedure was valid) was titrated at −5° with a standard solution of bromine in carbon tetrachloride, and required 2·42 g. of bromine ≡ 1·23 g. of *cyclo*hexene or 17·5%; *cyclo*hexene dibromide, b. p. 88°/10 mm., was obtained by fractional distillation of the resulting solution.

Acetoethylamide (0·5 g.) and phosphoric oxide (1 g.) in xylene (5 c.c.) were heated at 110° (bath temp.) while a slow stream of dry nitrogen was passed to carry the emergent gases through a dilute solution of bromine in ethanol. No ethylene dibromide was obtained [although, in a control experiment with ethanol as source, it was readily produced and was identified by conversion into bis-(2 : 5-dichlorophenylthio)ethane (Loudon and Shulman, *J.*, 1939, 1066)]. The phosphoric residue contained much tar, and basification of a concentrated aqueous extract yielded only a small amount (6%) of ethylamine, identified as 2 : 4-dinitrophenylethylamine, m. p. and mixed m. p. 112—114°.

In a similar experiment no propylene was produced from aceto-*n*-propylamide.

We are indebted to the Carnegie Trust for the Universities of Scotland for scholarships which enabled two of us (G. T. D. and D. E.) to participate in this work. We also acknowledge assistance in the practical work from Messrs. P. C. Arni, J. M. Daly, and G. Doig. Microanalyses were carried out by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, October 13th*, 1948.]

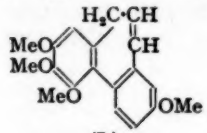
230. *Colchicine and Related Compounds. Part VIII. Preliminary Synthetic Experiments.*

By N. Barton, J. W. Cook, J. D. Loudon, and (in part) J. MacMillan.

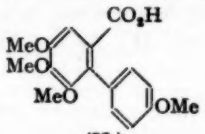
In connection with a project to synthesise colchinol methyl ether, the acid (III) has been prepared through the intermediary (II), obtained satisfactorily by a Gomberg–Hey type of reaction. Cyclisation of the bromo-acid (IV), obtained from (III), did not lead to seven-membered ring formation but was attended by displacement and migration of bromine. The resulting bromo-ketone (probably X) was reduced to 5 : 6 : 7-trimethoxy-4-*p*-methoxyphenyl-1-indanone (IX), identical with specimens obtained by direct cyclisation of (III).

2 : 3 : 4 : 7-Tetramethoxyfluorenone (VII), obtained by cyclisation of (II) and also from 4 : 5 : 6 : 4′-*tetramethoxydiphenic acid* (XII), was transformed by diazomethane into a mixture from which was isolated 2 : 3 : 4 : 7 : 9 (or 10)-*pentamethoxyphenanthrene* (XIII).

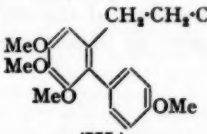
The chemical behaviour of deaminocolchinol methyl ether, described in Part V (Barton, Cook, and Loudon, *J.*, 1945, 176), led to the conclusion that this important degradation product of colchicine is 9 : 12 : 13 : 14-tetramethoxy-3 : 4 : 5 : 6-dibenz*cyclo*hepta-1 : 3 : 5-triene (I). The synthesis of dibenz*cyclo*heptatrienes and related compounds raises a general problem to which we are devoting attention, but the particular substitution pattern of (I) appeared to invite a more individual treatment on the lines described below; moreover, its successful issue would provide necessary information on the structure proposed (Part V) for colchinol methyl ether. The work described was substantially complete by June, 1946 (cf. Barton, Ph.D. Thesis, Glasgow, 1946), when it was already evident that this particular synthetic route did not lead to the desired objective, although at the time the point of deviation remained unsettled. Recently Frank, Fanta, and Tarbell (*J. Amer. Chem. Soc.*, 1948, **70**, 2314) have published an account of some equally inconclusive experiments along similar lines. Since our results differ from and supplement theirs in several notable respects and since we have now ascertained the point at which the projected synthesis miscarries, we record here the relevant features of our work together with a related synthesis of 4 : 5 : 6 : 4′-*tetramethoxydiphenic acid* (XII), itself a degradation product of colchicine.



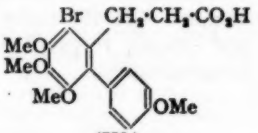
(I.)



(II.)



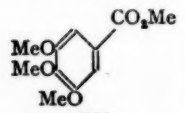
(III.)



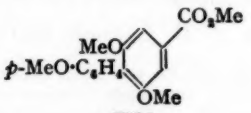
(IV.)

Like ourselves, the aforementioned authors have prepared the acids (II), (III), and (IV) and have attempted to cyclise the acid (IV) to the ketone (VIII), but, whereas in the preparative stages they achieved the union of the two aryl nuclei by appropriate crossed-Ullmann reactions and discarded as here impracticable the Gomberg–Hey type of reaction, the latter process in the form described by Elks and Hey (*J.*, 1943, 441) has given satisfactory results in our hands. Methyl 3 : 4 : 5-trimethoxybenzoate (V), condensed with 1-p-*methoxyphenyl*-3 : 3-*dimethyltriazen*, yielded the methyl ester of (II) together with a small quantity of a second *methyl* ester, $C_{18}H_{18}O_5$, which apparently results from displacement of one methoxyl group of (V) by the *p*-methoxyphenyl residue. The precise structure of this interesting by-product was not investigated, but the formation of analogous products by the interaction of (V) with other triazens has been observed in these laboratories, and, in view of the known mobility of the 4-methoxyl group in compounds related to (V) (cf. Asahina, *Ber.*, 1936, **69**, 1643; Richtzenhain, *ibid.*, 1944, **77**, 1; Haller and Schaffer, *J. Amer. Chem. Soc.*, 1939, **61**, 2175; Hurd and Winsberg, *ibid.*, 1942, **64**, 2085), the by-product is in all probability *methyl* 3 : 5-*dimethoxy*-4-p-*methoxyphenylbenzoate* (VI). In harmony with this view it was found that whereas the carboxylic *acid* obtained by saponifying the ester by-product yielded in normal fashion an acid chloride and *amide*, the acid (II) was rapidly converted by treatment with thionyl chloride into the fluorenone (VII)—a compound also described by Frank, Fanta, and Tarbell. In contrast to the findings of these authors, however, we found no difficulty in preparing the *hydrazide* of (II) and hence, by the method of McFadyen and Stevens (*J.*, 1936, 584), readily obtained the aldehyde (II; CHO for CO_2H), *viz.*, 3 : 4 : 5-*trimethoxy*-2-p-*methoxyphenylbenzaldehyde*. This aldehyde was condensed with malonic acid to yield the corresponding *cinnamic acid* from which by successive reduction and bromination the acids (III) and (IV) respectively were prepared.

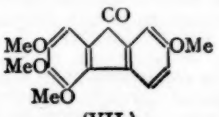
Frank, Fanta, and Tarbell have sufficiently emphasised the difficulties—which we also experienced—in cyclising the acid (IV). As product of a Friedel–Crafts reaction they describe



(V.)

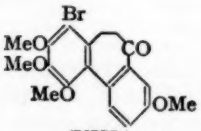


(VI.)

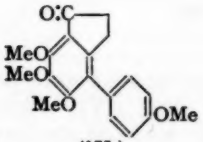


(VII.)

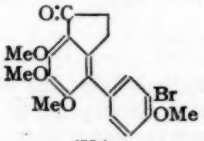
a bromo-ketone, m. p. 145° (corr.), which is probably identical with a bromo-ketone, m. p. 143° (uncorr.), obtained by us, although in our experience the latter compound was accompanied by a mono-demethylated *analogue* separable only with difficulty and of cryptophenolic nature. Our bromo-ketone was debrominated by hydrogen in presence of palladised strontium carbonate, and the resulting ketone was converted *via* its oxime into the corresponding primary amine which was characterised as the *picrate* and *acetyl* derivative. Deamination of the amine by the method of Cook and Graham (Part III, *J.*, 1944, 322; cf. Cook, Dickson, Ellis, and Loudon, Part VII, preceding paper) gave a product which, although insufficient in quantity for analysis, was definitely shown to be distinct from deaminocolchinol methyl ether (I). Moreover, model experiments having shown that dibenz*cyclo*heptadienones analogous to (VIII) are smoothly oxidisable to phenanthraquinones (Cook, Dickson, and Loudon, Part VI, *J.*, 1947, 746), the completely negative results obtained by applying this sensitive test to our bromo-ketone and its debromination product conclusively showed at this stage that neither of these ketones had the required 7-membered ring-structure of (VIII). Positive identification of our cyclisation products was retarded by a mistaken m. p. for the indanone (IX) which we had prepared by cyclisation of the acid (III) with anhydrous hydrofluoric acid. Frank, Fanta, and Tarbell, who report (*loc. cit.*, p. 2319) that (III) is not cyclised by this means, effected the ring-closure by an internal Friedel–Crafts reaction. The discrepancies of technique and melting point which thus became apparent caused us to re-examine both methods of cyclising (III) with the result that, whilst we confirmed the efficacy of hydrofluoric acid, we obtained by both methods the same product of m. p. approximating to the value recorded by the above authors. Furthermore, this product and the derived oxime were identical with the ketone and oxime respectively, obtained as described from (IV) by successive cyclisation and debromination.



(VIII.)



(IX.)



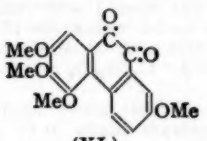
(X.)

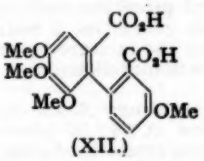
Taken in conjunction with the proof of structure advanced by Frank, Fanta, and Tarbell for the acid (IV), these results make it clear that cyclisation of this acid by the Friedel–Crafts reaction involves displacement and migration of the bromine substituent. The bromo-ketone so produced is formulated as (X) since on oxidation (see Experimental) it affords an acid which still retains the bromine, thereby excluding the alternative formula in which bromine has entered the methylene group adjacent to carbonyl.* Oxidation of the debrominated ketone, *viz.* (IX), yields an analogous *acid*, $C_{19}H_{20}O_7$. Frank, Fanta, and Tarbell do not record debromination of their bromo-ketone although they suggest that debromination was incidental in one attempt to cyclise (IV); the significance of the observation that the ill-defined product in this case was distinct from (IX) cannot be assessed at present.

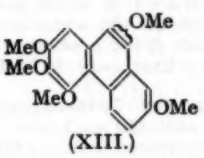
In Part V (*loc. cit.*), 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone (XI) was produced by oxidising deaminocolchinol methyl ether with sodium dichromate in acetic acid, and its synthesis was achieved by similar oxidation of the rather inaccessible 2 : 3 : 4 : 7-tetramethoxy-phenanthrene-9- and -10-carboxylic acids. It has now been shown that the phenanthraquinone is itself readily oxidised by hydrogen peroxide in presence of alkali to the corresponding *diphenic acid* (XII), and that this acid on distillation affords the fluorenone (VII). The reverse process, *viz.*, conversion of (VII) into (XI) and (XII), acquires considerable value from the accessibility

* *Note added in proof.* Since this paper was submitted, Huang, Tarbell, and Arnstein (*J. Amer. Chem. Soc.*, 1948, **70**, 4181) have likewise concluded that the bromo-ketone is (X).

of the fluorenone, through cyclisation of (II) as described above, and from the potentialities for further synthesis contained in the diphenic acid (XII). Accordingly expansion of the


(XI.)


(XII.)


(XIII.)

5-membered ring of (VII) to the 6-membered phenanthrene type was effected by reaction with diazomethane (cf. Schultz, Schultz, and Cochran, *J. Amer. Chem. Soc.*, 1940, **62**, 2902), and from the mixture so produced 2 : 3 : 4 : 7 : 9(or 10)-*pentamethoxyphenanthrene* (XIII) was isolated; this yielded (XI) on oxidation. More conveniently, the crude reaction products were oxidised directly and afforded an easily separable mixture of (XI) with regenerated fluorenone (VII).

Experimental.

1-p-*Methoxyphenyl*-3 : 3-*dimethyltriazen.*—*p*-Anisidine (100 g.) in concentrated hydrochloric acid (290 c.c.) and water (200 c.c.) was diazotised with a concentrated solution of sodium nitrite (56 g.) in water. The diazo-solution, kept at 0°, was added dropwise to a cooled and stirred mixture of dimethylamine (280 g.; 25%) and 30% aqueous sodium carbonate (800 c.c.). The resulting oil, stirred for 30 minutes following the addition, was extracted with benzene, dried (KOH), and recovered from the solvent. It distilled as a pale yellow liquid (110 g.), b. p. 150—152°/10 mm. (Found: N, 23·2. $C_9H_{13}ON_3$ requires N, 23·5%).

Methyl 3 : 4 : 5-*Trimethoxy*-2-p-*methoxyphenylbenzoate.*—The above triazen (56 g.) and methyl 3 : 4 : 5-trimethoxybenzoate (V) (280 g.) were slowly treated with acetic acid (72 c.c.) at 100°, and the whole was heated on the water-bath for 16 hours. The resulting dark liquid was dissolved in chloroform, and the solution was washed thoroughly with dilute hydrochloric acid, water, dilute sodium hydroxide, and water. After drying and recovery, distillation gave a few drops of anisole followed by the unchanged, solid ester (230 g.), b. p. 175—190°/10 mm. which was used directly for renewed reaction with triazen, and a residue. The latter, combined with corresponding residues from several runs, gave on fractionation (1) a small quantity of unchanged ester, b. p. 158—172°/1 mm.; (2) a slight intermediate oily fraction, b. p. 172—195°/0·8 mm.; (3) the main oily fraction, b. p. 195—206°/0·8 mm.; and (4) a small oily fraction, b. p. >206/1 mm. (some decomp.). Fractions (2) and (3), when rubbed with a little methanol and allowed to stand, deposited solids which crystallised together from methanol as a mixture of stout prisms (main constituent) and fine needles. Most of the needles were removed by swirling and decanting with the mother-liquor which was then used, with slight warming, to extract the remainder of the needles from the prisms, the process being repeated on further crops obtained by concentrating the methanol mother-liquors. These crystalline products were slightly augmented by redistilling the combined gums recovered from the various methanol solutions, and repeating the above treatment. In this way from 270 g. of the triazen there were obtained 75 g. of the prisms consisting of methyl 3 : 4 : 5-trimethoxy-2-(*p*-methoxyphenyl)benzoate, m. p. 74° (Frank, Fanta, and Tarbell, *loc. cit.*, give m. p. 63°) (Found: C, 64·9; H, 5·85. Calc. for $C_{18}H_{20}O_6$: C, 65·1; H, 6·0%), and 5·5 g. of the needles, provisionally regarded as *methyl* 3 : 5-*dimethoxy*-4-p-*methoxyphenylbenzoate* (VI), m. p. 133—134° from methanol (Found: C, 67·2; H, 5·7; OMe, 40·65. $C_{17}H_{18}O_5$ requires C, 67·5; H, 5·95; OMe, 41·1%).

The final methanol mother-liquors, when combined and heated with 50% sodium hydroxide, gave a non-saponifiable oil, which was extracted with ether and discarded, and a mixture of two acids which were separated by fractional crystallisation from methanol. The first crop formed prisms or flakes from methanol, m. p. 166—168° with previous softening, consisting of 3 : 4 : 5-trimethoxy-2-(*p*-methoxyphenyl)benzoic acid (II) (Found after drying at 100° in a vacuum: C, 64·45; H, 5·7. Calc. for $C_{17}H_{18}O_6$: C, 64·15; H, 5·7%), and converted by diazomethane in ether into the above methyl ester, m. p. and mixed m. p. 74°. The second, less abundant and less soluble, fraction formed long needles of 3 : 5-*dimethoxy*-4-p-*methoxyphenylbenzoic acid*, m. p. 227—228° from methanol (Found after drying at 100° in a vacuum: C, 66·6; H, 5·5; OMe, 32·55. $C_{16}H_{16}O_6$ requires C, 66·7; H, 5·6; OMe, 32·3%) converted (*a*) by diazomethane in ether into the above methyl ester, m. p. and mixed m. p. 133°, (*b*) by warming with an excess of thionyl chloride into an acid chloride which was obtained crude by distilling off the excess of reagent and yielded an *amide*, m. p. 232° from ethanol, on addition of concentrated ammonia (Found: C, 66·6; H, 5·65. $C_{16}H_{17}O_5N$ requires C, 66·9; H, 5·9%).

3 : 4 : 5-*Trimethoxy*-2-p-*methoxyphenylbenzaldehyde.*—A solution of methyl 3 : 4 : 5-trimethoxy-2-(*p*-methoxyphenyl)benzoate (14·6 g.) in methanol (30 c.c.) and 99% hydrazine hydrate (30 c.c.) was heated under reflux for 7½ hours. The *hydrazide* (13 g.) collected from the cooled solution after boiling with charcoal and augmented by concentration of the mother-liquor formed colourless rods, m. p. 154—155° from ethanol (Found: C, 61·5; H, 6·0. $C_{17}H_{20}O_5N_2$ requires C, 61·45; H, 6·0%). After being dried at 100° it (14 g.) was dissolved in dry pyridine (82 c.c.), benzenesulphonyl chloride (8·2 c.c.) was added at 0°, and the whole was kept—finally at room temperature—for 3 hours. The *benzenesulphonylhydrazide* (17·5 g.), obtained when the mixture was stirred into dilute hydrochloric acid, had m. p. 177·5—178·5° from methanol (Found: C, 58·25; H, 5·3. $C_{23}H_{24}O_7N_2S$ requires C, 58·5; H, 5·1%). It (14 g.) was dissolved in ethylene glycol (140 c.c.) at 160°, sodium carbonate (8·4 g.) was added in one lot, and the whole was vigorously stirred for 130 seconds before terminating the reaction by adding hot water (140 c.c.). The *aldehyde*, recovered from a chloroform extract of the cooled

mixture, crystallised as colourless prisms, m. p. 62—63° (6—7 g.) from methanol (Found: C, 67·4; H, 6·0. $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%).

3 : 4 : 5-*Trimethoxy*-2-p-*methoxyphenylcinnamic Acid*.—A solution of the above aldehyde (3 g.) in pyridine (6 c.c.) to which a few drops of piperidine had been added was heated with malonic acid (2·0 g., first on the water-bath (moisture guard) for 1 hour and then under reflux for 15 minutes. The product (2·9 g.), obtained by pouring the mixture on crushed ice and hydrochloric acid, formed colourless prisms, m. p. 187—188° from methanol (Found: C, 66·5; H, 6·2. $C_{19}H_{20}O_6$ requiresC, 66·3; H, 5·8%).

β-(3 : 4 : 5 : 4′-*Tetramethoxydiphenylyl*)*propionic Acid*.—A solution of the above acid (2·8 g.) in acetic acid (50 c.c.) was hydrogenated at 20° in presence of palladium black (0·17 g.). The product, recovered from the filtered solution, crystallised from methanol as colourless prisms, m. p. 103° (2·67 g.) (Found: C, 65·75; H, 6·3. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·4%).

β-(6-*Bromo*-3 : 4 : 5 : 4′-*tetramethoxydiphenylylpropionic Acid* (IV).—Solution of bromine (0·4 c.c.) in chloroform (10 c.c.) and of the above phenylpropionic acid (2·47 g.) also in chloroform (50 c.c.) were mixed and left at room temperature for 2 hours. The solution was washed with water until free from hydrobromic acid, and the recovered product was crystallised first from benzene–ligroin and then (2·9 g.) from methanol. It had m. p. 169—170° (Found: C, 53·3; H, 5·0. Calc. for $C_{19}H_{21}O_6Br$: C, 53·6; H, 4·9%). When heated with methanol in presence of a little concentrated sulphuric acid it formed a methyl ester which was isolated by distillation, b. p. 180—210° (air bath)/0·2 mm., and was crystallised from methanol; needle clusters, m. p. 90—91° (Found: C, 54·6; H, 5·25. Calc. for $C_{20}H_{23}O_6Br$: C, 54·7; H, 5·2%).

Cyclisation of Acid (IV).—A suspension of the bromo-acid (1 g.) in pure dry benzene (10 c.c.) was shaken with phosphorus pentachloride at room temperature under moisture guard until it had completely dissolved (about 1 hour). Volatile material was removed by warming (*ca.* 60°) under reduced pressure and finally by evacuation at room temperature (1 hour). The residual, usually crystalline, acid chloride [micro-m. p. 91—93° (from ligroin)] was dissolved in carbon disulphide (2 c.c.), finely ground fresh aluminium chloride (0·8 g.) was added, and the whole, protected from moisture, was left with occasional shaking at 0° for 2 days. After addition of some dilute hydrochloric acid and removal of the solvent in steam the crude product was worked up in one of two ways:

(*a*) A chloroform extract was washed with dilute sodium carbonate (from which original bromo-acid, *ca.* 0·25 g., of very variable quality was recovered and purified through its methyl ester) and then with sodium hydroxide solution (which removed some phenolic, but not cryptophenolic material, see below). The product (0·75 g.), recovered from the dried chloroform solution, distilled at 180—200° (air bath)/0·4 mm., yielding half its weight of a distillate (charring and resinification) in which the presence of cryptophenolic material was shown by a violet colour with ferric chloride in aqueous methanol. This constituent was best separated by passing a solution of the distillate in benzene through a column of alumina which retained the cryptophenol, while the benzene eluate afforded on evaporation pale yellow rods of the required *product*, m. p. 143—143·5° (softening 140°) (from benzene–ligroin), giving a negative ferric chloride test (Found: C, 56·2; H, 4·8. $C_{19}H_{19}O_5Br$ reqires C, 56·0; H, 4·7%).

(*b*) The crude product was extracted with ether in which it partly dissolved. The ethereal solution was washed as above with sodium carbonate and sodium hydroxide solutions, dried, and evaporated. The residual gum (0·225 g.), which gave no ferric chloride reaction, was dissolved in benzene and recovered as a pink glass (0·20 g.) after pasing through a column of alumina. It was directly employed for debromination (cf. below) with good results. The ether-insoluble fraction, which remained as a white solid suspended in the aqueous layer, was extracted with chloroform, washed with the same alkali washings as used for the ether solution, dried, recovered (0·50 g.), and purified by dissolving it in benzene and passing the solution through a column of alumina. The benzene eluate contained some of the above fully methylated material, m. p. 143°, while demethylated product was retained on the column and was washed out by means of benzene to which some methanol had been added. This *compound* formed pale yellow prisms, m. p. 149—150° from methanol, depressed to micro-m. p. *ca.* 135° by admixture with the product of m. p. 143°. It was quite insoluble in aqueous sodium hydroxide and only sparingly soluble in aqueous alcoholic sodium hydroxide, and gave a violet colour with ferric chloride in aqueous methanol (Found: C, 54·9; H, 4·5. $C_{18}H_{17}O_5Br$ requires C, 55·0; H, 4·3%). When methylated by heating (7 hours) with methyl sulphate and potassium carbonate in dry benzene, followed by purification (alumina), it gave the above ketone, m. p. and mixed m. p. 141—143°, in small yield.

Although the yields varied, the above processes, with minor modifications, gave a 10—15% yield of fully methylated product and a similar quantity of mono-demethylated product. Modifications—employing nitrobenzene as solvent, extended reaction time, higher reaction temperature, aluminium bromide as condensing agent—all failed to give better results, and a sparingly soluble, neutral product of m. p. 348—350° from benzene–nitrobenzene was often encountered and possibly resulted from polymerisation (Found: C, 55·3; H, 4·9%). Attempted ring-closure by means of concentrated sulphuric acid was impracticable owing to sulphonation, and the use of phosphoric oxide in boiling xylene gave a crystalline product of micro-m. p. 110—111° (Found: C, 62·9; H, 3·9%) which did not yield a dinitrophenylhydrazone and was not further examined.

Oxidation of the Bromo-ketone, $C_{19}H_{19}O_5Br$.—The bromo-ketone (0·15 g.) and sodium dichromate (1 g.) in aqueous acetic acid were heated under reflux for 1 hour. After cooling, dilution with water, and extraction with ether, the product was separated by dilute sodium hydroxide into neutral and acidic fractions. The former, recovered from the ether solution, consisted of unchanged bromo-ketone (0·05 g.), m. p. and mixed m. p. 143°, there being no trace of a (coloured) phenanthraquinone. The acidic fraction, recovered in ether from the acidified aqueous solution, had m. p. 216° from dilute acetic acid. Although it was not obtained analytically pure (Found: C, 52·7; H, 4·6. Calc. for $C_{18}H_{19}O_7Br$: C, 51·9; H, 4·3%) it was probably the bromo-derivative of the acid similarly obtained from the debrominated ketone (below).

5 : 6 : 7-*Trimethoxy*-4-p-*methoxyphenyl*-1-*indanone* (IX).—*Cyclisation of* (III). A solution of (III) (0·20 g.) in anhydrous hydrogen fluoride (4 c.c.) was allowed to evaporate in absence of moisture. The

resulting gum was dissolved in ether and, after being washed with dilute sodium hydroxide and recovered, formed colourless prisms, m. p. 86°, from methanol, identical with a sample, m. p. and mixed m. p. 85—86° (oxime, m. p. and mixed m. p. 219°), obtained by Friedel–Crafts cyclisation as described by Frank, Fanta, and Tarbell (*loc. cit.*) who give corrected m. p. 89° (oxime, m. p. 217° decomp.).

Debromination of (X). A solution of the bromo-ketone (0·10 g.) in methanol (30 c.c.) was shaken with 2% palladised strontium carbonate in an atmosphere of hydrogen for 3—4 hours. The debrominated ketone, recovered from the filtered solution, distilled between 160° and 175° (air bath)/0·2 mm. and had m. p. and mixed m. p. 84—85° (Found: C, 69·4; H, 6·0. Calc. for $C_{19}H_{20}O_5$: C, 69·5; H, 6·1%). It formed an oxime, m. p. and mixed m. p. 218—219° (Found: C, 66·6; H, 6·2. Calc. for $C_{19}H_{21}O_5N$: C, 66·5; H, 6·1%). In an earlier experiment with a specimen of the bromo-ketone contaminated with cryptophenolic material, the product from the above treatment yielded long colourless prisms which gave a deep violet colouration with ferric chloride in aqueous methanol and had m. p. 122—123° from methanol: it was probably the monodemethylated *product* of the above ketone (Found: C, 68·4; H, 5·8. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%).

Oxidation. A sample of (IX) (obtained by debromination), when oxidised as described for the bromo-ketone, was partly recovered unchanged and partly converted into a carboxylic *acid*, (micro-) m. p. 166—168° (from chloroform then benzene–petroleum) (Found: C, 63·4; H, 5·5. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·55%).

1-*Amino*-5 : 6 : 7-*trimethoxy*-4-p-*methoxyphenylindane.*—The oxime of (IX) (0·2 g.) dissolved in ethanol (70—80 c.c.) was hydrogenated (4 hours) at 80—90°/60—65 atmospheres in presence of Raney nickel (0·2 g.). After filtration and recovery from the solvent, the product was dissolved in ether from which by addition of picric acid in ether the *picrate* was precipitated, m. p. 216—220° (with darkening) from methanol (Found: C, 53·7; H, 4·6. $C_{19}H_{23}O_4N,C_6H_3O_7N_3$ requires C, 53·8; H, 4·6%). When the gummy base, regenerated from the picrate, was rubbed with concentrated hydrochloric acid, it gave the *hydrochloride* as clusters of fine white rods, m. p. 211—212°, from moderately strong hydrochloric acid (Found: C, 62·3; H, 6·4. $C_{19}H_{23}O_4N,HCl$ requires C, 62·4; H, 6·6%). The base, regenerated from its hydrochloride, was acetylated by allowing it to stand with acetic anhydride (½ hour) and then shaking the mixture with 2N-sodium hydroxide. The *acetyl* derivative formed colourless prisms, m. p. 180—181° (Found: C, 68·0; H, 6·8; OMe, 33·8. $C_{21}H_{25}O_5N$ requires C, 67·9; H, 6·75; OMe, 33·4%).

Deamination. The acetyl derivative (20 mg.) was heated for 20 minutes with phosphoric oxide (40 mg.) in dry xylene (1 c.c.). The gum, recovered from the decanted solution, was partly purified by passing its solution in benzene through alumina. Recovery from the eluate and subsequent distillation gave a non-basic product, b. p. 140—145° (air bath)/0·2 mm., which had (micro-) m. p. 70—72° from methanol. There was insufficient material for analysis, but the compound was probably 4 : 5 : 6-trimethoxy-7-*p*-methoxyphenylindene.

[With J. MacMillan] 4 : 5 : 6 : 4′-*Tetramethoxydiphenic Acid* (XII).—2N-Sodium hydroxide (0·18 c.c.) was added (10 minutes) with shaking to a suspension of 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone (XI) (56 mg.) in methanol (1 c.c.) containing 30% hydrogen peroxide (0·12 c.c.). Since the solid did not completely dissolve on warming, more hydrogen peroxide (0·12 c.c.) was added until dissolution was complete (about 1 hour). The methanol was distilled off, the resulting precipitate was dissolved by addition of water, and the solution was clarified by filtration through kieselguhr and made acid to Congo-red. The *acid*, recovered from chloroform, formed colourless prisms from aqueous alcohol, m. p. 240—241° after sublimation (210—220°/0·3 mm.) (Found: C, 59·7; H, 4·95. $C_{18}H_{18}O_8$ requires C, 59·7; H, 5·0%).

2 : 3 : 4 : 7-*Tetramethoxyfluorenone* (VII).—(*a*) A solution of 3 : 4 : 5-trimethoxy-2-*p*-methoxyphenylbenzoic acid (0·5 g.) in thionyl chloride (1·5 c.c.) was gently warmed (10 minutes) on the water-bath; excess of thionyl chloride was distilled off, and the solid residue was obtained as matted brick-red needles from methanol, m. p. 115° (Found: C, 67·8; H, 5·3. Calc. for $C_{17}H_{16}O_5$: C, 68·0; H, 5·3%). (*b*) The same compound, m. p. 108—110° from methanol and mixed m. p. 110—111°, was obtained when the above tetramethoxydiphenic acid was heated for 10 minutes in a "Pyrex" tube at 350—360°. The product formed a red distillate, collected by cutting the tube and recovery from benzene solution after washing with dilute sodium carbonate.

Ring-enlargement of 2 : 3 : 4 : 7-*Tetramethoxyfluorenone* (VII).—A cooled solution of the fluorenone (0·5 g.) in ether (20 c.c.) and methanol (40 c.c.) was slowly treated with a large excess of diazomethane in ether, and the mixture was kept first for 2 hours at 0° and then for 12 hours at room temperature. The dark red gum (0·56 g.), recovered from the solution, was treated as follows in separate experiments:

(*a*) By means of aqueous sodium hydrogen carbonate it was separated into an acidic (0·05 g.) and a non-acidic (0·49 g.) gum. A solution of the latter in benzene–petroleum (1 : 1), when passed through a column of alumina, produced a chromatogram of two colourless fluorescent bands separated by a broad pink band. These were eluted in turn and afforded after recovery (i) 2 : 3 : 4 : 7 : 9(or 10)-*pentamethoxyphenanthrene* (XIII) (0·24 g.) as colourless needles, m. p. 115—117° from methanol (Found: C, 69·6; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%); (ii) unchanged tetramethoxyfluorenone (0·045 g.), m. p. and mixed m. p. 112—113°; (iii) a colourless gum (0·2 g.). On separate oxidation (compare *b*) fraction (i) gave the phenanthraquinone (XI); fraction (iii) gave the fluorenone (VII); while the acidic gum gave a mixture of (XI) and (VII) which was separated by chromatography.

(*b*) The red gum (1 g.) in acetic acid (14·5 c.c.) was slowly treated with a solution of sodium dichromate (2·9 g.) in acetic acid (2·9 c.c.) and water (1·5 c.c.), and the mixture was heated under reflux for 45 minutes, cooled, and diluted with water. The product was extracted with benzene, the extract being washed with dilute sodium hydroxide, dried, and evaporated. A solution of the resulting gum in benzene–petroleum (3 : 2) was passed through a column of alumina from which, by elution with benzene, a broad orange band afforded the fluorenone (VII; 0·385 g.), while the subsequent eluate of a violet-red band gave the phenanthraquinone (XI; 0·285 g.), m. p. and mixed m. p. 192—194° (diazine from *o*-phenylenediamine, m. p. and mixed m. p. 176—177°).

We are indebted to Imperial Chemical Industries Ltd. (Dyestuffs Division) for enabling one of us (N. B.) to participate in this work, and we also thank the Department of Scientific and Industrial Research for a Maintenance Allowance (to J. M.). The microanalyses were by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, October 13th*, 1948.]

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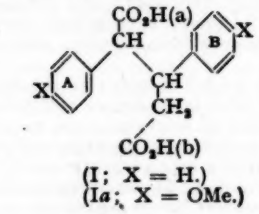
231. *Polycyclic Aromatic Hydrocarbons. Part XXXIV. Cyclisation of αβ-Diphenylglutaric Anhydride.*

By G. M. BADGER, (MISS) J. E. CAMPBELL, and J. W. COOK.

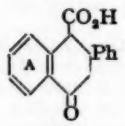
Cyclisation of the anhydride of αβ-diphenylglutaric acid (I) with aluminium chloride gave *α-phenyl-α-indan-3-on-1-ylacetic acid* (V) and not the expected tetralone (II), together with some 3-hydroxy-1 : 2-benzfluorenone (III). Treatment with caustic alkali partly converted this acid (V) into a *stereoisomeride*. Both acids have been transformed, by a series of reactions, into isomeric 1-*phenyltetrahydroacenaphthenes* (X), the structures of which have been established by conversion into (XI), through 1-*phenylacenaphthene*.

IN connection with a project to synthesise dihydroxyperhydrochrysenes we have been interested in developing new routes to *s*-hexahydrochrysene derivatives which might serve as intermediates. The excellent method of Ramage and Robinson (*J.*, 1933, 607; 1938, 397) enables *s*-hexahydrochrysenes to be obtained in both *cis*- and *trans*-forms, but suffers from the disadvantage that poor yields are obtained in the preparation of the intermediate ββ′-diaryladipic acids. It seemed possible that derivatives of 3-phenyltetral-1-one-4-carboxylic acid (II) suitable for our purpose could be obtained by cyclisation of αβ-diarylglutaric acids (I, I*a*), which are readily available by the Michael condensation of arylacetic esters with arylcinnamic esters. αβ-Diphenylglutaric acid (I) is known in all four possible optically active forms (Avery and Maclay, *J. Amer. Chem. Soc.*, 1929, **51**, 2833), the two (±)-forms having m. p.s 231° and 208°. The higher-melting acid is obtained preferentially by the Michael reaction between ethyl phenylacetate and ethyl cinnamate, and we have found that it is readily converted by acetic anhydride into the anhydride of the lower-melting acid.

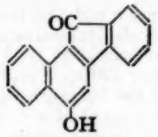
When this anhydride was treated with anhydrous aluminium chloride in nitrobenzene solution, it was transformed into a keto-acid. From the work of von Braun and his collaborators (see Johnson, " Organic Reactions," Vol. II, p. 116), who showed that such cyclisations give six- in preference to five-membered rings, it was to be expected that this keto-acid would have the desired structure (II). Some support was lent to this view by the fact that when the internal Friedel–Crafts reaction was conducted without ice-cooling there was also isolated a small amount of a bright red ketone which was shown to be 3-hydroxy-1 : 2-benzfluorenone (III). This was identified by conversion into its acetate and into 3-acetoxy-1 : 2-benzfluorene (Cook and Preston, *J.*, 1944, 559), and it could clearly arise by further cyclisation of (II) followed by dehydrogenation under the influence of aluminium chloride.



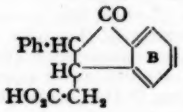
(I; X = H.)
(I*a*; X = OMe.)



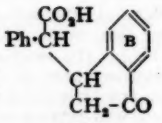
(II.)



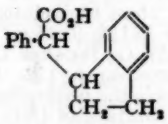
(III.)



(IV.)



(V.)



(VI.)

When, however, the chloride of the pure keto-acid was treated with aluminium chloride (III) was not formed, and the keto-acid itself was unaffected by anhydrous hydrogen fluoride. This cast doubt on the validity of the assumption that the keto-acid formed from the anhydride of (I) was represented by the structure (II), and further investigation showed that the reaction had in fact given, not the tetralone derivative (II), but an indanone derivative (V). Five-membered

ring formation involves reaction of ring B of (I) rather than ring A, and could lead to two alternative structures, (IV) or (V), depending upon which carboxyl group furnishes the carbonyl group. Structure (IV) was excluded, for the keto-acid gave a *benzylidene* derivative.

Intramolecular acylation may lead to a five-membered ring when an alternative six-membered ring is possible if there are activating substituents in the aromatic ring which is concerned in the process. This result does not seem to have been observed hitherto in the cyclisation of saturated acids in the absence of such activation, although it is known that if unsaturation is present in the carbon chain five-membered rings may be formed preferentially (compare Stobbe and Vieweg, *Ber.*, 1902, **35**, 1727; Haworth and Sheldrick, *J.*, 1935, 636; Cook and Preston, *loc. cit.*). There appears to be no reason why cyclisation of the carboxyl group (*b*) in (I) on to ring A should be inhibited by steric influences, and it is probable that the determining factor is a deactivation of ring A by the carboxyl group (a). It is consistent with what is known of the rapidity with which an inductive effect becomes damped in passing along a saturated carbon chain that the deactivating effect of this carboxyl group on ring (A), which requires transmission through only one carbon atom, completely outweighs the deactivating effects of both carboxyl groups on ring (B). Such effects would have to be transmitted through two saturated carbon atoms.

The formation of (V) to the exclusion of (IV) is also of interest. This involves cyclisation of carboxyl group (b), adjacent to a secondary carbon atom, on to ring B, rather than cyclisation of carboxyl group (a), which adjoins a tertiary carbon atom. Analogous effects have been observed by Haworth (*J.*, 1932, 1128), who found that in the Friedel–Crafts reaction between naphthalene and methylsuccinic anhydride in nitrobenzene solution the carboxyl group which adjoins the methylene group becomes attached to the aromatic nucleus, and by Robinson and Young (*J.*, 1935, 1414), who record a similar result in the condensation of phenylsuccinic anhydride with veratrole, also in nitrobenzene solution. Superficially, this might be compared with the similar orientating influence of the methyl group and the phenyl group (to which attention has been drawn, for example, by Grieve and Hey, *J.*, 1933, 968), in spite of the circumstance that the methyl group is electron-repelling and the phenyl group is intrinsically electron-attracting (compare Ingold, *Chem. Reviews*, 1934, **15**, 239). Such an interpretation would, however, be an unwarranted generalisation, inconsistent with other recorded results.

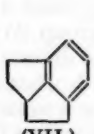
Thus, phenylsuccinic anhydride reacts with benzene at the carboxyl group adjacent to the tertiary carbon atom (Anschütz, Hahn, and Walter, *Annalen*, 1907, **354**, 148) whereas 2 : 4-dimethoxyphenylsuccinic anhydride and resorcinol dimethyl ether give about equal amounts of the two isomeric keto-acids (Rice, *J. Amer. Chem. Soc.*, 1931, **53**, 3159). Mixtures of isomerides are also formed in the Friedel–Crafts reaction between methylsuccinic anhydride and benzene or toluene (Mayer and Stamm, *Ber.*, 1923, **56**, 1424). It is to be noted that in none of the cases just cited was nitrobenzene used as a solvent. Possibly this influences the course of the reactions, for it is known that in Friedel–Crafts reactions with naphthalene and phenanthrene and their derivatives the nature of the solvent has considerable influence in determining the positions of substitution.

The structure of the product of cyclisation of (I) as *α-phenyl-α-indan-3-on-1-ylacetic acid* (V) was established by a series of transformations which we have carried out. This keto-acid (designated as isomeride-A) was dimorphic and had m. p.s 154—155° and 170—171°. Hydrolysis of its *methyl* ester with alcoholic alkali gave not only the original acid but also an isomeric *keto-acid* (isomeride-B), m. p. 225—226°. The higher-melting acid was likewise formed by the prolonged action of boiling aqueous-alcoholic alkali on the lower-melting acid. Only isomeride-B was isolated from the hydrolysis of its *methyl* ester, but some isomeride-A may have been present in the non-crystalline acidic material which was also formed. Clearly the two keto-acids are stereoisomeric.

Clemmensen reduction of these gave, respectively, *α-phenyl-α-1-indanylacetic acid*-A and *α-phenyl-α-1-indanylacetic acid*-B, both of which may be represented by structure (VI). The former acid (VIA) could not be dehydrogenated with sulphur or palladium, and it was recovered unchanged after attempted cyclisation with anhydrous hydrogen fluoride; an internal Friedel–Crafts reaction gave a non-acidic gum without carbonyl reactivity. Attempted dehydrogenation with palladium of the homologue (VIII) described below was also unsuccessful. These negative results are in accord with the structure (V) for the keto-acid from which (VI) was obtained, but cannot be reconciled with structure (II) which should give a naphthalene derivative by dehydrogenation of the reduced acid, and the latter should undergo ready cyclisation to a tetrahydrobenzfluorenone. On the other hand, dehydrogenation of (VI) would not be expected under the conditions used, and the failure to undergo cyclisation is in harmony with previous failures to

prepare the highly strained tricyclic system (VII) which would be present in the only cyclic ketone that (VI) could give (compare v. Braun *et al.*, *Ber.*, 1917, **50**, 56; 1928, **61**, 956; 1929, **62**, 145).

Chain lengthening of the stereoisomeric acids (VI) by the Arndt–Eistert procedure gave β-*phenyl*-β-1-*indanylpropionic acid*-A and β-*phenyl*-β-1-*indanylpropionic acid*-B (VIII). It was not found possible to convert this A-acid into the stereoisomeride (B) by prolonged boiling of its methyl ester with alkali. The two acids were cyclised by anhydrous hydrogen fluoride to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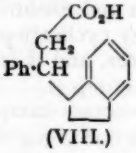
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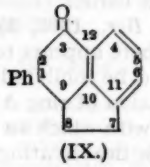
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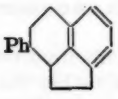
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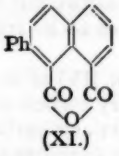
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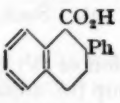
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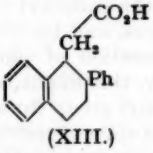
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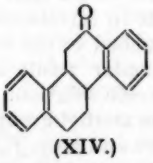
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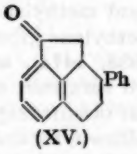
(XV.)

stereoisomeric 3-*keto*-1-*phenyl*-1 : 2 : 3 : 9-*tetrahydroacenaphthenes* (IX, A and B). Cyclisation of the acid-A (VIII) was also accomplished by treatment of its chloride with aluminium chloride or stannic chloride.

Reduction of the ketone-A (IX) by Clemmensen's method gave 1-*phenyl*-1 : 2 : 3 : 9-*tetrahydroacenaphthene*-X (X), m. p. 71°, but reduction by the Huang–Minlon modification (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) of the Wolff–Kishner method gave in addition an isomeric 1-*phenyl*-1 : 2 : 3 : 9-*tetrahydroacenaphthene*-Y (X), m. p. 59°. Reduction of ketone-B (IX) by the latter method gave only 1-phenyltetrahydroacenaphthene-Y. The isomerisation of ketone-A during alkaline reduction is surprising and difficult to interpret in view of the remoteness of the carbonyl group from an asymmetric centre. The possibility is not excluded that in one of the hydrocarbons the ring carrying the phenyl group has become aromatic owing to double-bond migration.

Both hydrocarbons (X) were smoothly dehydrogenated to the same 1-*phenylacenaphthene*, the structure of which was confirmed by oxidation to the known 2-phenyl-1 : 8-naphthalic anhydride (XI).

The isolation of two parallel series of stereoisomerides of (V), (VI), (VIII), (IX), and (X) provides decisive evidence in favour of structure (V) for the cyclisation product of (I) and constitutes the final link in the chain of evidence against structure (II). If the latter structure were correct then its reduction product would be (XII) and the subsequent homo-acid (XIII). Newman (*J. Amer. Chem. Soc.*, 1938, **60**, 2947) has synthesised the *cis*-form of (XIII) and has cyclised it to *cis*-2-ketohexahydrochrysene (XIV). From the work of Ramage and Robinson (*loc. cit.*) it is to be expected that the *trans*-form of (XIII) would cyclise to the unknown *trans*-2-ketohexahydrochrysene (XIV), but the possibility that steric factors might lead to (XV) cannot be excluded, and reduction of (XV) would give the structure (X) which results from the route through (V). The isolation of two stereoisomeric homologues of (V) effectively disposes of this possibility, for if the alternative structure (XIII) were correct one of the isomerides would necessarily be Newman's *cis*-acid and would cyclise to his *cis*-ketone (XIV). This possibility is excluded by m. p. comparisons with our products.

Experimental.

αβ-Diphenylglutaric Anhydride.—Condensation of ethyl phenylacetate (100 g.) and ethyl cinnamate (100 g.) by heating under reflux for 2½ hours with sodium ethoxide (from 4 g. of sodium and 60 c.c. of ethanol) (compare Borsche, *Ber.*, 1909, **42**, 4496) gave a theoretical yield of αβ-diphenylglutaric esters, from which the higher-melting isomeride (140 g.) was isolated by recrystallisation from ethanol.

Hydrolysis with potassium hydroxide (175 g.) in boiling 50% ethanol (2340 c.c.) for 9 hours gave αβ-diphenylglutaric acid, m. p. 230—231° (110 g.). This acid was heated under reflux for 8 hours with acetic anhydride (500 c.c.). After concentration under reduced pressure, αβ-diphenylglutaric anhydride was collected and recrystallised from chloroform–light petroleum. It formed colourless crystals, m. p. 125—126° (90 g.). Avery and Maclay (*loc. cit.*), who prepared the anhydride from the same acid by heating under pressure with acetyl chloride, give m. p. 126·5°.

α-Phenyl-α-indan-3-on-1-ylacetic Acid-A (V).—Aluminium chloride (40 g.) was added gradually to a stirred ice-cold solution of αβ-diphenylglutaric anhydride (35 g.) in nitrobenzene (400 c.c.). After the addition was complete, the stirred mixture was allowed to warm to room temperature, and the reaction was then allowed to proceed for 60 hours. After decomposition with ice and hydrochloric acid, the nitrobenzene was removed in steam and the residue recrystallised from methanol. *α-Phenyl-α-indan-3-on-1-ylacetic acid*-A, thus obtained, formed colourless needles, m. p. 154—155° (20 g.) (Found: C, 76·4; H, 5·1. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%). A fused specimen, after resolidification, was found to have m. p. 170—171°, and the specimen, m. p. 154—155°, was also converted into the higher-melting form by prolonged heating at 100°. The higher-melting form (Found: C, 77·0; H, 5·6%) was also obtained by recrystallisation from ethyl acetate. Three recrystallisations of the higher-melting form from methanol, gave the lower-melting form.

The 2 : 4-*dinitrophenylhydrazone* formed orange-red needles from acetic acid, m. p. 261° (decomp.) (Found: C, 62·0; H, 4·1. $C_{23}H_{18}O_6N_4$ requires C, 61·9; H, 4·1%). The *benzylidene* derivative crystallised from acetic acid in pale yellow prisms, m. p. 185—186° (Found: C, 81·1; H, 5·3. $C_{24}H_{18}O_3$ requires C, 81·4; H, 5·1%). The *methyl* ester, prepared from the acid with methanol and dry hydrogen chloride, formed colourless needles (from methanol), m. p. 99—100° (Found: C, 76·75; H, 5·5. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·75%).

α-Phenyl-α-indan-3-on-1-ylacetic Acid-B.—The above methyl ester (1·2 g.) was hydrolysed by heating under reflux for 1 hour with potassium hydroxide (2 g.) in ethanol (15 c.c.) and water (5 c.c.). The solution became highly coloured, sometimes dark red, blue, or green. Addition of hydrochloric acid gave a gummy precipitate which was crystallised from methanol. The first crop (0·1 g. to 0·3 g. in different runs) was recrystallised and gave *α-phenyl-α-indan-3-on-1-ylacetic acid*-B as colourless crystals, m. p. 225—226° (Found: C, 76·8; H, 5·2%). A small amount of the original acid, m. p. 154—155° was also obtained from the liquors, but the yield of the two crystalline products never exceeded 50%, the remainder being an uncrystallisable gum. The new acid, m. p. 225—226°, was also obtained, in small yield, when the acid, m. p. 154—155°, was heated under reflux with potassium hydroxide in aqueous alcohol for various periods.

The *methyl* ester of the acid, m. p. 225—226°, was prepared with methanolic hydrogen chloride. It formed colourless prisms (from methanol), m. p. 138—139° (Found: C, 77·2; H, 5·8%). Hydrolysis of this ester gave only the higher-melting acid in crystalline form, together with an oily acidic material.

The 2 : 4-*dinitrophenylhydrazone* of the acid formed orange needles, m. p. 284—285° (decomp.) (from nitrobenzene) (Found: C, 61·7; H, 3·9%).

3-*Hydroxy*-1 : 2-*benzfluorenone* (III).—This was obtained in an experiment in which aluminium chloride was added to a solution of αβ-diphenylglutaric anhydride in nitrobenzene, without ice-cooling. Recrystallisation of the crude acidic product gave a small amount (0·12 g.) of red insoluble material. It was almost insoluble in benzene, acetone, and methanol, but was recrystallised from a large volume of acetic acid. Sublimation at 210°/0·5 mm., and recrystallisation from acetic acid, gave red needles, m. p. 304—310° (decomp.). They gave a violet-red solution in dilute sodium hydroxide, being reprecipitated by acid, and a green solution in concentrated sulphuric acid. These properties are in conformity with the formulation of the compound as 3-hydroxy-1 : 2-benzfluorenone (Found: C, 82·8; H, 4·2. Calc. for $C_{17}H_{10}O_2$: C, 82·9; H, 4·1%). It was further identified by acetylation with acetic anhydride to give 3-acetoxy-1 : 2-benzfluorenone, m. p. 185—186°, and by reductive acetylation to give 3-acetoxy-1 : 2-benzfluorene, m. p. 157—158°. Both acetyl compounds were identified by direct comparison with authentic specimens (Cook and Preston, *loc. cit.*; Fierz-David and Jaccard, *Helv. Chim. Acta*, 1928, **11**, 1042).

α-Phenyl-α-1-indanylacetic Acid-A (VI).—Water (18 c.c.), concentrated hydrochloric acid (44 c.c.), toluene (25 c.c.), α-phenyl-α-indan-3-on-1-ylacetic acid-A (2·5 g.), and acetic acid (5 c.c.) were added, in the order named, to granulated amalgamated zinc (compare Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438) and the mixture was heated under reflux vigorously for 24 hours. Further portions (each of 12·5 c.c.) of concentrated hydrochloric acid were added at intervals of 6 hours. The product (10 g.), which crystallised from the toluene on cooling and from a benzene extract of the aqueous layer on concentration, was recrystallised from benzene–light petroleum (b. p. 60—80°). *α-Phenyl-α-1-indanylacetic acid*-A formed colourless needles, m. p. 141—142° (Found: C, 81·0; H, 6·3. $C_{17}H_{16}O_2$ requires C, 81·0; H, 6·4%).

α-Phenyl-α-1-indanylacetic Acid-B.—α-Phenyl-α-indan-3-onylacetic acid-B (m. p. 225—226°) was reduced as above, except that (owing to the insolubility of the acid) anisole was used instead of toluene. *α-Phenyl-α-1-indanylacetic acid*-B formed colourless prisms, m. p. 153—154° (from benzene) (Found: C, 81·1; H, 6·1%).

β-Phenyl-β-1-indanylpropionic Acid-A (VIII).—A mixture of ice-cold anhydrous benzene (8 c.c.), pyridine (2 drops), thionyl chloride (5 c.c.), and α-phenyl-α-1-indanylacetic acid-A (1·25 g.) was allowed to warm to room temperature during ½ hour, and was then warmed to 40° for ½ hour. The excess of thionyl chloride and benzene were removed in a vacuum on the water-bath. The residue, dissolved in a little benzene, was decanted from the pyridine hydrochloride and added dropwise to an ethereal solution (*ca.* 200 c.c.) of diazomethane (from 3 g. nitrosomethylurea; *Org. Synth.*, Coll. Vol. 2, p. 165), previously dried over potassium hydroxide pellets. During the addition, the flask was cooled in a freezing mixture, and the contents stirred mechanically. After a further ½ hour's stirring, the solution was left overnight. The solvent was allowed to evaporate spontaneously, and the yellow residue was dissolved in dioxan (15 c.c.) and heated on the water-bath with 20% ammonium hydroxide (20 c.c.) and 10% aqueous silver nitrate (10 c.c.) until evolution of nitrogen was complete. A silver

mirror normally formed on the walls of the vessel. The mixture was then boiled with charcoal, and filtered. *β-Phenyl-1-β-indanylpropionamide* (0·9 g.) formed colourless needles, from alcohol, m. p. 151—152° (Found: C, 81·5; H, 7·1; N, 5·5. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%). Hydrolysis of the amide (1 g.) was effected by 12 hours' boiling with potassium hydroxide (1 g.) in alcohol (25 c.c.) and water (2 c.c.). *β-Phenyl-β-1-indanylpropionic acid*-A formed colourless prisms, m. p. 123—125° (from dilute acetic acid) (Found: C, 81·3; H, 6·7. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%).

β-Phenyl-β-1-indanylpropionic Acid-B.—α-Phenyl-α-1-indanylacetic acid-B was converted into the acid chloride and treated with diazomethane as described for the above isomeride-A. In this case, however, it was found preferable to isolate the *diazo-ketone*. It formed yellow needles (from benzene), m. p. 126—128° (decomp.) (Found: N, 10·2. $C_{19}H_{16}ON_2$ requires N, 10·2%). Attempts to prepare a crystalline amide or ester from this product were unsuccessful. It was found, however, that a pure acid could be obtained from a crude ester, and the following procedure was adopted. The diazo-ketone (0·5 g.) in methanol (18 c.c.) was treated with a slurry of silver oxide (from 2 g. of silver nitrate) and methanol (10 c.c.), in portions. When the reaction had subsided, the mixture was heated under reflux for 1 hour, boiled with charcoal, and filtered. The filtrate was concentrated to 15 c.c., and potassium hydroxide (1·25 g.) was added. After heating under reflux for 1 hour, the mixture was acidified, and extracted with ether. The oil obtained on removal of the ether crystallised from light petroleum to which a little chloroform was added. Further crystallisation from light petroleum gave *β-phenyl-β-1-indanylpropionic acid*-B (0·2 g.) as small colourless prisms, m. p. 104—105° (Found: C, 81·2; H, 6·6%).

3-*Keto*-1-*phenyl*-1 : 2 : 3 : 9-*tetrahydroacenaphthene*-A (IX).—(i) The above phenylindanylpropionic acid-A (1 g.) was treated with excess of thionyl chloride and benzene in the usual way, and the solution evaporated in a vacuum. The product, in dry benzene (16 c.c.), was treated at room temperature with aluminium chloride (0·6 g.) in portions. The temperature was kept between 30° and 50° for 3 hours, after which the mixture was decomposed with ice and hydrochloric acid. Removal of the benzene gave 3-*keto*-1-*phenyl*-1 : 2 : 3 : 9-*tetrahydroacenaphthene*-A (0·6 g.), which formed small colourless prisms, m. p. 101—102° (from alcohol) (Found: C, 87·0; H, 6·2. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%).

The 2 : 4-*dinitrophenylhydrazone* formed small scarlet prisms, from chloroform, m. p. 249—250° (Found: C, 67·4; H, 4·5. $C_{24}H_{20}O_4N_4$ requires C, 67·3; H, 4·7%).

The same ketone (0·75 g.) was obtained (ii) when the acid (1 g.) was treated with anhydrous hydrogen fluoride, and the reagent allowed to evaporate from a platinum crucible fitted with a lid; and also (iii) when stannic chloride (0·5 c.c.) in dry benzene (0·5 c.c.) was added to a solution of the acid chloride (from the acid, 0·5 g.; benzene, 5 c.c.; and phosphorus pentachloride, 0·45 g.).

3-*Keto*-1-*phenyl*-1 : 2 : 3 : 9-*tetrahydroacenaphthene*-B (IX).—Cyclisation of phenylindanylpropionic acid-B with hydrogen fluoride was carried out as described for the A-isomeride. 3-*Keto*-1-*phenyl*-1 : 2 : 3 : 9-*tetrahydroacenaphthene*-B formed colourless prisms, m. p. 139—140°, from alcohol (Found: C, 86·9; H, 6·3%). Its 2 : 4-*dinitrophenylhydrazone* formed small dark red prisms, m. p. 229—230°, from chloroform (Found: C, 67·3; H, 4·7%).

1-*Phenyl*-1 : 2 : 3 : 9-*tetrahydroacenaphthene* (X).—(i) The above ketone-A (1 g.) and hydrazine hydrate (0·5 c.c.; 85%) were added to a solution of sodium (0·25 g.) in ethylene glycol (10 c.c.). After 1 hour's heating under reflux, the condenser was removed, and the heating continued until the temperature of the contents of the flask reached 195—200°. Refluxing was then continued for 3 hours. After cooling, the mixture was acidified and extracted with benzene. Removal of the solvent and recrystallisation from alcohol gave a first crop of 1-*phenyltetrahydroacenaphthene*-Y (X) which after further recrystallisation formed long colourless needles, m. p. 59—60° (Found: C, 92·1; H, 8·0. $C_{18}H_{18}$ requires C, 92·3; H, 7·7%). Concentration of the liquors gave a mixture of the above needles together with some hexagonal prisms. The latter were separated by hand, and on recrystallisation from methanol, 1-*phenyltetrahydroacenaphthene*-X (X) was obtained as colourless prisms, m. p. 71—72° (Found: C, 92·3; H, 7·5%). A mixed m. p. with the Y-isomeride was 38—42°.

(ii) A small yield of the X-isomeride was also obtained by reduction of the ketone-A by the Clemmensen method. The m. p. (68—70°) was not depressed by admixture with the specimen obtained as above. A mixture of this hydrocarbon with a specimen of *cis*-hexahydrochrysene (XIV), m. p. 73—74°, had m. p. 40—45°.

(iii) The above ketone-B, when reduced by the Wolff–Kishner method as described for the ketone-A, gave only 1-phenyltetrahydroacenaphthene-Y, which was identified by direct comparison with the specimen obtained as above. No trace of the X-isomeride was observed.

1-*Phenylacenaphthene*.—1-Phenyltetrahydroacenaphthene-Y (0·34 g.) was dehydrogenated by heating at 290—300° with palladium black (0·05 g.) in an atmosphere of carbon dioxide until no more hydrogen was evolved (4 hours). 1-*Phenylacenaphthene* (0·2 g.) formed colourless leaflets, m. p. 105—106° (Found: C, 93·8; H, 6·0. $C_{18}H_{14}$ requires C, 93·9; H, 6·1%).

Dehydrogenation of 1-phenyltetrahydroacenaphthene-X was carried out in the same way, and the product was shown by mixed m. p. to be identical with that obtained above.

2-*Phenyl*-1 : 8-*naphthalic Anhydride*.—A solution of the above 1-phenylacenaphthene (0·2 g.) in acetic acid (3·5 c.c.) was treated with sodium dichromate (1·4 g.) slowly, and with shaking. The mixture was heated under reflux for 2 hours, poured into warm water, cooled, and filtered. Extraction with boiling sodium carbonate solution containing a little sodium hydroxide, precipitation with acid, and sublimation at 240° at ordinary pressure gave 2-phenyl-1 : 8-naphthalic anhydride as pale yellow crystals, m. p. 238—239°, from acetic acid (Found: C, 79·1; H, 3·6. Calc. for $C_{18}H_{10}O_3$: C, 78·8; H, 3·7%). Koelsch and Rosenwald (*J. Amer. Chem. Soc.*, 1937, **59**, 2166) report m. p. 239—240°.

One of us (G. M. B.) has been working with an I.C.I. Research Fellowship, and we also thank the D.S.I.R. for a Maintenance Allowance (to J. E. C.). Microanalyses have been carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

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232. *Mechanism of Aromatic Side-chain Reactions with Special Reference to the Polar Effects of Substituents. Part XIV. The Aldehyde–Cyanohydrin Reaction with Halogeno-benzaldehydes: Polar Effects of Halogen Substituents.*

By JOHN W. BAKER and H. B. HOPKINS.

As one section of a joint attack, in collaboration with Hughes, Ingold, and Kohnstam, of University College, London, on the problem of the polar effects of halogen substituents (X = F, Cl, Br, I), the values of the equilibrium constants ($K = k_2/k_1$) and of the individual velocity coefficients k_1 and k_2 in the reaction

$$m\text{- or } p\text{-X}\cdot C_6H_4\cdot CHO + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X\cdot C_6H_4\cdot CH(OH)\cdot CN$$

have been determined in constant boiling-point alcohol as solvent at 20°, using the technique of Baker and Hemming (*J.*, 1942, 191). *m*- and *p*-Nitrobenzaldehydes have been included in the investigation, as examples of substituents of unequivocal electron-attraction, earlier data for alkyl substituents providing information regarding electron-release substituents.

The values of K decrease in the order, *p*-alkyl > *p*-F > H > *p*-Cl > *p*-NO_2 > *p*-Br > *p*-I > *m*-NO_2 ~ *m*-F > *m*-I > *m*-Cl > *m*-Br, *p*-F thus exhibiting an overall electron-*release* effect, whilst the remaining halogens (including *m*-F) show an overall electron-attraction which is in the reverse order to that required by the operation of the $-I$ effect alone. Analysis of the data proves that the halogens exhibit both inductive ($-I$) and mesomeric ($+M$) effects which decrease in the order F ⋙ Cl > Br > I, and that there is considerable second-order relay of the $+M$ effect from the *m*-position.

The velocity data for both k_1 and k_2 show that all the halogens (fluorine included) exert an overall electron-attraction in both the *m*- and the *p*-position but that again the inductive order is inverted or upset by the superimposition of a mesomeric electron-release, reduced both in the transition state and in the cyanohydrin owing to the diminution of unsaturation in the side chain.

Although the results can be satisfactorily interpreted on the basis of the operation of these two polar effects alone, yet the incidence of an inductomeric electron-*attraction*, decreasing in the order I > Br > Cl > F, is not excluded as an alternative explanation of the k_2 sequence.

THE present position regarding our understanding of the polar effects of halogen substituents is far from satisfactory. A comprehensive review has been given by one of us elsewhere (Hopkins, Thesis, University of Leeds, 1948).

There is general agreement, based on fairly extensive physical and chemical evidence, for the operation of an electron-attracting inductive ($-I$) effect, derived from the dipole $\overset{\delta+}{C}\text{–}\overset{\delta-}{Hal}$, which decreases in the order, originally postulated by Ingold (*Chem. Reviews*, 1934, **15**, 237), F > Cl > Br > I.

Information regarding any corresponding polarizability (inductomeric) effect is more meagre, but it is highly probable that the polarizability of the C–Hal bond decreases in the reverse order I > Br > Cl > F: the decreasing molecular refractivities of this bond, *viz.*, Hal = I, 14·51: Br, 9·47: Cl, 6·57: F, 1·82 c.c. (Remick, "Electronic Interpretations of Organic Chemistry," p. 79), may be cited as one piece of evidence for this conclusion.

Superimposed on these electrostatic effects is the tautomeric electron-release by halogen substituents arising from conjugation of the unshared electron-pairs with attached, unsaturated centres. The original suggestion that both the permanent (mesomeric) and polarizability (electromeric) effects should increase in the order F < Cl < Br < I (Ingold, *loc. cit.*, p. 242) has required modification in the light of later work and there is sound evidence, which is fully substantiated by the present investigation, for the conclusion that the order of mesomeric electron-release follows the reverse sequence F > Cl > Br > I. On the physical side, an accurate determination of the mesomeric moments of the halogenobenzenes by Audsley and Goss (*J.*, 1942, 497) gave the values F, 1·04; Cl, 0·95; Br, 0·75; I, 0·51 D., thus confirming the order obtained earlier by Groves and Sugden (*J.*, 1937, 1992) on a somewhat different basis of computation. The same order of mesomeric electron-release was revealed by an examination of the dissociation constants of halogenated phenols and anilines by Bennett, Brooks, and Glasstone, (*J.*, 1935, 1821), who, in one case (that of *p*-fluorophenol which is a weaker acid than phenol itself) found that fluorine exhibited an overall electron-release, the $+M$ effect being sufficiently powerful to reverse the direction of the polarization arising from the strong $-I$ effect of this substituent.

In the examination of the effect of halogen substituents on the velocity of side-chain reactions a complex situation is present. Quite apart from the possible incidence of duplex polar

requirements (*e.g.*, the electrostriction of a nucleophilic reagent and the elimination of an anion) when the reaction is of the S_N2 type, the observed polar effects of halogen substituents may be the resultant of both polarization and polarizability effects originating from both tautomeric (electron-release) and inductive (electron-attraction) mechanisms. Examination of the more important data (Baddeley and Bennett, *J.*, 1933, 261; 1935, 1819; Olivier, *Rec. Trav. chim.*, 1922, **41**, 301, 646; 1923, **42**, 516, 775; Bennett and Brynmor Jones, *J.*, 1935, 1815; Norris, Fasce, and Staud, *J. Amer. Chem. Soc.*, 1935, **57**, 1415; Nixon and Branch, *ibid.*, 1936, **58**, 492, 2499; Ingold and Nathan, *J.*, 1936, 222; Kindler, *Annalen*, 1926, **450**, 1; Baker, *J.*, 1936, 1448; Davies and Lewis, *J.*, 1934, 1599; Braude and Stern, *J.*, 1947, 1096) shows that, with but two minor exceptions (referred to below), the overall effect of all halogen substituents, as a group, in both *m*- and *p*-positions, is always one of electron-*attraction*. Regarding the relative effects of individual halogens within the group, it is found that the order of overall electron-attraction, as revealed by the velocity order (sometimes confirmed by the Arrhenius E values for the reaction), may be either a complete *reversal* of the $-I$ order, F > Cl > Br > I, or, more often, a partly inverted, "mixed" order. In the hydrolysis of *p*-halogeno-benzyl chlorides in 50% aqueous acetone (Bennett and Jones, *loc. cit.*) the *p*-fluoro-compound, unlike the other halogen derivatives, was found to undergo hydrolysis at a faster rate than the parent, unsubstituted compound, indicating, in this case, an overall electron-release by fluorine. It has, however, already been pointed out (Baker, *Trans. Faraday Soc.*, 1941, **37**, 632) that, under the conditions employed, the reaction is probably largely unimolecular (S_N1) and hence the operation of a large electromeric electron-release effect by fluorine might be expected. The second reaction in which *all* the halogens apparently exhibit a small, overall electron-release effect is the addition of pyridine to the halogenobenzyl bromides in dry acetone (Baker, *loc. cit.*). This reaction was proved to be bimolecular (S_N2) and one in which a minimum velocity occurs in a graded polar series of substituents showing increasing electron-release. Moreover the velocity differences are so small (maximum range $10^4k^{30°}$ = H, 1·22; F, 1·48) that it is unsafe to draw definite conclusions from them.

Examination of the effect of halogen substituents on the velocity of electrophilic substitution in the same aromatic nucleus, *e.g.*, the nitration of halogenobenzenes (Bird and Ingold, *J.*, 1938, 918) and the halogenation of halogenobenzenes and 1-halogenonaphthalenes (De la Mare and Robertson, *J.*, 1948, 100) reveals the incidence of a polarizability electron-release effect by the halogen substituent which seems to decrease in the order I > Br > Cl > F. This effect was originally regarded by Bird and Ingold as an electromeric (+ E) effect, whilst De la Mare and Robertson recognised also the alternative possibility that an inductomeric effect might be responsible. Unpublished data of Hughes, Ingold, and Kohnstam (see below) have cast further doubt upon the interpretation given by Bird and Ingold and, at present, the nature of this polarizability effect is best left an open question.

This brief review of the present position reveals a close analogy to that which pertained to the polar effects of alkyl groups before the introduction, by Baker and Nathan (*J.*, 1935, 1844), of the concept of partial conjugation of the shared electrons of a C–H bond with an attached unsaturated centre—the phenomenon now generally known as hyperconjugation. In the search for conclusive experimental evidence for this new concept two types of reaction were proved to be of great value. Hughes, Ingold, and Taher (*J.*, 1940, 949) found, in the unimolecular solvolysis of *p*-alkylbenzhydryl chlorides, a reaction which is very favourable for the dominant operation of the electromeric electron-release effect, and Baker and Hemming (*J.*, 1942, 191) showed that a clear-cut verification of the theoretical order of mesomeric electron-release could be derived from a study of the cyanohydrin equilibria of *p*-alkylbenzaldehydes. It was considered that these same two reactions, applied to the corresponding halogen-substituted compounds, might provide similarly clear-cut evidence regarding the order of the electromeric (+ E) and mesomeric (+ M) effects, respectively, of the halogens. Accordingly, by mutual arrangement, a joint attack on the halogen problem was planned with Professors Ingold and Hughes, and the present communication describes the results of an investigation of both the position of equilibrium, $K = k_2/k_1$, and the separate values of k_1 and k_2 in the reaction

$$X\cdot C_6H_4\cdot CHO + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X\cdot C_6H_4\cdot CH(OH)\cdot CN,$$

where X = F, Cl, Br, and I in the *m*- and *p*-positions. The complementary examination of the solvolysis of the *m*- and *p*-halogenobenzhydryl chlorides will be published in due course by Hughes, Ingold, and Kohnstam.

The experimental technique employed and the method for the evaluation of k_1 and k_2 are those previously described by Baker and Hemming (*loc. cit.*). Since, theoretically, the resultant polar effect of halogen substituents might be one either of electron-release or of electron-attraction, it is obviously desirable to " bracket " the halogen group by a study of the effects of unequivocally electron-releasing and electron-attracting substituents. Data for the former are already available from the earlier study of *p*-alkylbenzaldehydes, and information regarding the latter has been obtained by inculsion of *m*- and *p*-nitrobenzaldehydes in the present investigation. Values for K (but not for k_1 and k_2) for the cyanohydrin formation of these two aldehydes have previously been published by Lapworth and Manske (*J.*, 1928, 2533), but we find that, in these cases, the cyanohydrin reaction is complicated by side reactions (possibly of the aldol condensation type). With both *m*- and *p*-nitrobenzaldehyde, addition of only *one* drop of tri-*n*-propylamine catalyst causes the rapid development of an intense orange-yellow colour, and the concentration of free hydrogen cyanide at first diminishes to a minimum value and thereafter rises continually. Obviously a true equilibrium is not attained. Better results were obtained by using the less powerful " velocity " catalyst (0·01M-pyridine + 0·01M-pyridinium benzoate) and, under such conditions, true equilibrium is attained (and maintained) with the *m*-nitro-compound, and the value quoted in Table I was

TABLE I.

Data for the reaction $X\cdot C_6H_4\cdot CHO + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X\cdot C_6H_4\cdot CH(OH)\cdot CN$ in constant-boiling alcohol at 20°. Equilibrium catalyst = 2 drops (~0·02 g.) of NPr_3 in 50 ml. of a solution initially ~2M with respect to both aldehyde and HCN. Velocity catalyst = 0·01M-pyridine + 0·01M-pyridinium benzoate. Units: g.-mol. l.$^{-1}$ sec.$^{-1}$.

X =	*p*-Me.	H.	F.		Cl.		Br.		I.		NO_2.	
			p.	*m*.	*p*.	*m*.	*p*.	*m*.	*p*.	*m*.	*p*.	*m*.
10^3K, g.-mol. l.$^{-1}$	8·98 ±0·13	4·45 ±0·13	6·30 ±0·13	2·13 ±0·02	3·85 ±0·12	1·97 ±0·01	3·26 ±0·05	1·88 ±0·02	3·13 ±0·04	2·02 ±0·04	3·4	2·1
$10^{-2}\Delta F$, cals.	27·5	31·6	29·5	35·9	32·4	36·3	33·4	36·6	33·6	36·2	33·1	35·9
10^5k_1, g.-mol. l^{-1}. sec.$^{-1}$	0·82* —	±0·02	3·59 ±0·01	10·22 ±0·02	6·94 ±0·04	12·45 ±0·02	9·14 ±0·07	14·32 ±0·16	9·38 ±0·09	14·5 ±0·3	37·0	58·4
$10^{10}k_2$, sec.$^{-1}$	0·74*	0·74*	2·26	2·18	2·67	2·45	2·98	2·69	2·94	2·92	12·6	12·3

(*p*-Bu^t 0·57*)

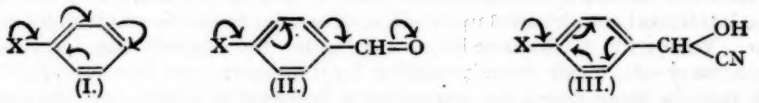
* The value now obtained for k_1 for benzaldehyde itself is rather lower than that (1·96) previously recorded by Baker and Hemming; hence, to make the k_1 and k_2 values for the *p*-Me compound comparable with the new data, their value has been multiplied by the factor 1·65/1·96. This correction does not alter the relative position of the values for alkyl groups in the graded polar series.

thus determined. With *p*-nitrobenzaldehyde a slower, but definite increase in free hydrogen cyanide concentration still occurs after the minimum value is reached, but with the weaker catalyst, this upward drift is approximately linear with time and the " equilibrium " concentration of free hydrogen cyanide was estimated by extrapolation of this straight-line portion to zero time. The value so obtained was slightly lower than the experimentally observed minimum concentration. The value of 10^3K thus obtained for the *m*-nitrobenzaldehyde equilibrium (2·10) is rather lower than that recorded by Lapworth and Manske (2·74), but the discrepancy is in the same direction and of the same order of magnitude as has been observed for all the K values we have determined, which are consistently rather lower than those of Lapworth and Manske (cf. also results in the *p*-alkyl series, *loc. cit.*). Our value for the *p*-nitro-compound (3·4) differs greatly from that of Lapworth and Manske (18·1). These authors, using one drop of tri-*n*-propylamine as catalyst, made no mention of any " drift " in the hydrogen cyanide concentration; indeed they state that " among all the cases . . . . investigated, that of *o*-nitrobenzaldehyde was the only one in which there was considerable irregularity in the amount of uncombined hydrogen cyanide present *after standing for several days* " (italics ours). In our experience the complicating side reactions would, in such a period, have released free hydrogen cyanide far in excess of the minimum and, presumably, true cyanohydrin equilibrium concentration (see Experimental, p. 1097), and would thus account for their much larger value of K.

The values obtained for the equilibrium constants K and the velocity coefficients k_1 and k_2 for all the compounds now studied are collected in Table I, earlier data for benzaldehyde and *p*-tolualdehyde being included for purposes of comparison.

DISCUSSION.

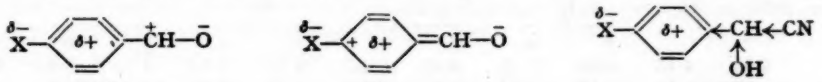
Equilibrium Data.—It is important to recognise that the mesomeric effect of a halogen substituent in the benzene ring, although a permanent polarization, will vary in magnitude from compound to compound. The delocalisation of the unshared electrons on a halogen in a monohalogenobenzene (I), where conjugation is restricted to the limits of the benzene ring,



(I.) (II.) (III.)

will be less than in (II), where a group in the *p*-position (such as $-CH{:}O$) extends the conjugation to the limits of the side chain since, in the latter case, the electrons can occupy greater configurational space with the consequent lowering of their energy and resonance stabilisation of the molecule. Thus, by arguments exactly similar to those given by Baker and Hemming (*loc. cit.*), the $+M$ effect of a *p*-halogen substituent should stabilise the free aldehyde (II) relative to benzaldehyde itself, to a greater extent than it does the cyanohydrin (III) relative to benzaldehyde cyanohydrin, with a resultant increase in the value of $K = k_2/k_1$. The greater the mesomeric effect of the halogen the larger should be the value of K and the smaller the value of the free-energy change calculated from the usual relationship $\Delta F = -RT \ln K$.

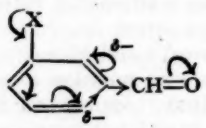
Superimposed on the mesomeric effect will be the inductive electron-attraction ($-I$) of the halogen. This gives rise to a fractional positive charge in the benzene ring which will oppose electron-duplet displacements $C\overset{\curvearrowright}{=}O$ in the aldehyde side chain. Consequently, structures of the general types (IV) and (V) will be of smaller significance in the structure of the halogeno-



(IV.) (V.) (VI.)

benzaldehyde (X = halogen) than they are in benzaldehyde itself (X = H). Thus the $-I$ effect of the *p*-halogen should be to destabilise the free aldehyde relatively to the parent benzaldehyde. In the cyanohydrin (VI) the $-I$ effect of the halogen might stabilise the molecule (relatively to benzaldehyde cyanohydrin) by increasing the energy required for the separation of CN as an anion, or it might destabilise it by lowering the energy necessary for proton separation from the OH group. In either case its effect on the cyanohydrin is likely to be much less significant than is its destabilising effect on the free aldehyde, so that the $-I$ effect of the halogen should decrease the value of K relatively to that of benzaldehyde.

The data in Table I show an order of K = *p*-Me > *p*-F > H > *p*-Cl > *p*-Br > *p*-I ~ *p*-NO_2. Hence, of the four halogens in the *p*-position, Cl, Br, and I exhibit an overall electron-*attraction*, which decreases in the order I > Br > Cl, but fluorine exhibits an overall electron-*release* since, like alkyl substituents, it has a K value > H. Hence the $+M$ effect of fluorine must be sufficiently large to overcome and reverse the polarization of its strong $-I$ effect. Similar arguments apply to the *m*-halogeno-substituted benzaldehydes, except that the $-I$ effect should be of smaller magnitude whilst the $+M$ effect would be greatly reduced since it cannot now reach the aldehyde side chain directly. There may, however, be a second-order effect arising from a relay of permanent, fractional negative charges on the two *o*-carbon atoms of the ring:



The data in Table I indicate that such second-order relay of the mesomeric effect, whilst not sufficient, even with fluorine, to reverse the overall electron-attraction due to the $-I$ effect (as it *does* in the *p*-fluoro-compound), does upset the $-I$ order of electron-attraction by the halogen substituents. Thus the K values for the *m*-series are in the order H > *m*-NO_2 ~ *m*-F > *m*-I > *m*-Cl > *m*-Br. Since all the halogens have K values < H, they must exhibit an overall electron-attraction which decreases in the order *m*-Br > Cl > I > F. The probable value of K for the *p*-nitro-derivative is greater than that for *m*-nitro-. It is difficult to conceive that the electron-attraction of a *p*-NO_2 group is weaker than that of *m*-NO_2, and a more plausible

explanation is found in the suggestion by Lapworth and Manske (cf. Ingold, *Ann. Reports*, 1928, **25**, 147) that there is a minimum value for K, now located at the *m*-bromo-compound, and that further increase in electron-attraction (*m*- and *p*-NO_2) again causes an increase in K. The overall electron-release of *p*-F makes it unlikely that its position in the *m*-series (close to *m*-NO_2) is due to strong electron-attraction. A much more satisfactory and consistent explanation is that the strong second-order relay of the large $+M$ effect of fluorine from the *m*-position, whilst not sufficient to reverse the direction of polarisation due to its $-I$ effect, *is* able to diminish its overall electron-attraction to such an extent that it becomes the least strongly electron-attracting of all the halogens in the *m*-position. Similarly the $+M$ effect of chlorine displaces it relatively to its neighbour bromine. On this view we have a self-consistent series of increasing electron attraction :

$$\underbrace{p\text{-alkyl} < p\text{-F}}_{\text{Electron release}} < \text{H} < p\text{-Cl} < p\text{-Br} < p\text{-I} < m\text{-F} < m\text{-I} < m\text{-Cl} < \underset{\text{Min. } K}{m\text{-Br} > m\text{-NO}_2} < p\text{-NO}_2$$

in which the inductive order of electron-attraction by halogens is completely reversed in the *p*-position by the superimposition of a strong $+M$ effect, and, in the *m*-position, becomes partly inverted and " mixed " owing to the modifying influences of a second-order relay of the $+M$ effect.

From the arguments developed above it is evident that the value of K_p/K_m should be larger the greater is the $+M$ effect of the halogen substituent. The experimental values of this ratio are :

X =	H.	F.	Cl.	Br.	I.
K_p/K_m =	1	2·98	1·96	1·73	1·55

a clear-cut proof that the order of the $+M$ effect is F > Cl > Br > I.

Velocity Data.—Interpretation of the velocity data is, of necessity, more complex since account must now be taken of relevant polarizability effects. The overall, base-catalysed reactions may be formulated

$$\text{B} \curvearrowright \text{H—CN} \curvearrowright \quad \text{CHAr=O} \curvearrowright \text{HB} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \overset{+}{\text{B}}\text{H} \quad \text{NC—CHAr—O—H} \curvearrowright \text{B}$$

In the forward reaction (left to right), the more difficult, rate-determining factor might be either the formation of the C–CN bond or the polarization of the C=O group, the former being facilitated by electron-attraction by the aryl group and the latter by its electron-release, especially by the tautomeric mechanism. The experimental values for k_1 (Table I) show that the forward reaction is retarded by electron-releasing alkyl groups and strongly accelerated by electron-attracting nitro-groups. Hence it may be safely assumed that the electrostriction of the CN′ ion is the more important energy requirement.

In the *p*-series the order $k_1 = p\text{-Me} < \text{H} < \text{F} < \text{Cl} < \text{Br} \gtrsim \text{I} \ll \text{NO}_2$ shows that the halogens, fluorine included, all exhibit an overall electron-attraction which decreases in the order $\text{I} \lesssim \text{Br} > \text{Cl} > \text{F}$, which is the reverse of that required by their $-I$ effects. Hence, as in the equilibrium data, there is a superimposed electron-release effect which must decrease in the order F > Cl > Br > I and which, although unable to reverse the polarisation due to the $-I$ effect, is able so to reduce it that fluorine shows a resultant minimum electron-attraction and, in the other halogens, completely inverts the inductive order. Such electron-release effect must be either tautomeric or inductomeric in character, but since the latter almost certainly decreases in the order I > Br > Cl > F (cf. p. 1089) the effect here operative is most probably tautomeric in character. In any reaction of the type A + B ⟶ C the transition state much more closely resembles C than it does A + B, *i.e.*, the transition state in the cyanohydrin reaction, $\text{Ar·CH}\overset{\delta-}{\text{=}}\text{O}$ will approximate more closely to that of the cyanohydrin $\text{Ar·CH(CN}^{\delta-}\text{)—O}^-$ in which the conjugation of the *p*-halogen substituent is largely restricted to the confines of the benzene ring (III). Hence the magnitude of the $+M$ effect in the *p*-halogenobenzaldehydes themselves probably approximates to a maximum displacement of the

unshared electron-pair so that, in the transition state, it becomes greatly reduced, *i.e.*, in the reaction the halogens are exhibiting a kind of $-(+E)$ effect. The resultant tautomeric effect still decreases in the order F > Cl > Br > I.

In the *m*-series the $-I$ effects will be somewhat reduced and the tautomeric effect greatly reduced, the argument being similar to that already given for the equilibrium data. The observed order is $k_1 = H < F < Cl < Br \gtrsim I \ll NO_2$, which again reveals an over-all electron-attraction by all halogen substituents, decreasing in the order $I \gtrsim Br > Cl > F$, the $-I$ order being inverted by superimposition of a second-order relay of the mesomeric effect. The ratio k_1^m/k_1^p should be larger the larger is this second-order relay: the values are as follows:

X =	H.	F.	Cl.	Br.	I.
k_1^m/k_1^p =	1	2·86	1·79	1·56	1·54

a series which clearly resembles that for K_p/K_m (p. 1093) and confirms the order of mesomeric electron-release F > Cl > Br > I.

Before leaving discussion of the k_1 data, it should be noted that the very strong electron-attraction of the *p*-NO_2 substituent causes a *decrease* in the value of k_1 relatively to that of the *m*-nitro-compound. It is evident that, in the latter compound, a condition has been reached when the induced positive charge on the carbonyl carbon has become so great that the polarization of the carbonyl group $C\overset{\curvearrowright}{=}O$ is now the more important factor energetically. Further increase in this induced positive charge, in the *p*-nitro-compound, thus causes a decrease in the velocity of the forward reaction. This constitutes another example of the condition where, in a graded polar series, the substituent acts first as if it is facilitating one requirement in an S_N2 mechanism and then, beyond a certain point, as if it were hindering the other (cf. Baker, *Trans. Faraday Soc.*, 1941, **37**, 637; Hughes, Ingold, and Shapiro, *J.*, 1936, 228).

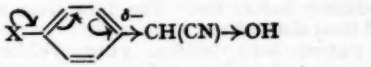
Considerable caution is necessary in any attempt to interpret the significance of the k_2 data. In the first place, the experimental values themselves are likely to be less accurate since, from their method of determination $k_2 = Kk_1$, all the errors in both k_1 and K are incorporated as their products. A second difficulty is the uncertainty of ascertaining what is, energetically, the determining factor in the back reaction. Experimentally, the velocity coefficient k_1 is determined by the loss in concentration of free cyanide ion, and this ion ceases to be precipitated as silver cyanide as soon as it has become united in the ion Ar·CH(CN)·$\bar{O}$ of the cyanohydrin. Since the cyanohydrin is, presumably, a very weak acid, the anion would be expected rapidly to attack a proton, but this would have no further effect on the concentration of free cyanide ion present in the system. Theoretically, however, there must exist the equilibrium Ar·CH(CN)·$\bar{O}$ + $\overset{+}{H}$ $\rightleftharpoons$ Ar·CH(CN)·OH, even though this equilibrium may be displaced well to the right. If the rate of decomposition of the *ion* of the cyanohydrin into cyanide ion and free aldehyde is very rapid compared with the rate of its formation by ionisation of the cyanohydrin, this latter equilibrium may never be attained during the course of the formation of the cyanohydrin from the free aldehyde, and the factor which is most important in determining the value of k_2 might thus become the ionisation of hydrogen from the OH group of the cyanohydrin. The alternative possibility would be that the rate-determining factor is the breaking of the C–CN bond to give free cyanide ion. On the first hypothesis k_2 should be increased by electron-attraction in the aryl group, but on the second the back reaction should be facilitated by electron-release.

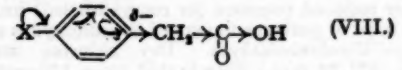
The data in Table I show that k_2 increases in the order *p*-alkyl $\ll$ H < *m*- and *p*-halogen < *m*-NO_2 < *p*-NO_2, a sequence which clearly suggests facilitation by electron-attracting substituents in the phenyl nucleus and which thus makes it extremely improbable that the main energetic requirement could be the breaking of the C–CN bond. In fact, in its broad outlines, the sequence is exactly the same as that found for k_1 where *electrostriction* of the cyanide ion is the important feature. It can therefore be concluded that the main energetic requisite for the back reaction is the ionisation of the hydrogen from the OH bond in the cyanohydrin, the energy required for the rupture of the C–CN bond being derived largely from the covalency sharing of the unshared electron-pair on the oxygen atom in the ion of the cyanohydrin $\overset{\curvearrowright}{\bar{O}}—C—\overset{\curvearrowright}{C}N$. Quite apart from such a theoretical interpretation, the experimental sequence clearly shows that all the halogens, in both *m*- and *p*-positions, are exerting an overall electron-attraction. The differences between the k_2 values for the various halogens, however, are very much smaller than are those for k_1 and, moreover, very little differentiation is observed between

halogen substitution in either the *m*- or the *p*-position. In so far as the small velocity differences are significant, the orders of the k_2 values are :

$$m\text{-halogen}: \quad I > Br > Cl > F > H$$
$$p\text{-halogen}: \quad I \sim Br > Cl > F > H$$

which, in both cases, must also represent the order of decreasing overall electron-attraction. This order is precisely the same (though with much smaller differences) as that deduced for the k_1 values which has been shown (p. 1093) to receive a consistent explanation on the basis of a $+T$ effect decreasing in the order $F > Cl > Br > I$ superimposed on the $-I$ effect which decreases in the same order. On the basis of the hypothesis that the important factor is the breaking of the O–H bond, any $+T$ effect would be one of inhibition and hence must be mesomeric and not electromeric in character. The only way in which such a mesomeric effect could reach the O–H bond in the cyanohydrin would be by inductive relay along the side chain from the phenyl nucleus (VII), and it would thus suffer very appreciable damping and could, possibly,

(VII.) 

 (VIII.)

so modify the electron-attracting influence of the halogens that the differences in their $-I$ effects were more or less obliterated, all halogens thus exerting an overall electron-attraction of closely similar magnitudes from either the *m*- or *p*-positions. It is not without significance that there are only small differences between the effect of the various halogens and between their effects in the *m*- and *p*-positions, on the dissociation constants of the phenylacetic acid series given in Table II (Dippy, *Chem. Reviews*, 1939, **25**, 207). In this closely similar system (VIII) the analogy extends to the nitro-group.

TABLE II.

Values of 10^5K *for halogeno-substituted phenylacetic acids in aqueous solution.*

Position of substituent.	H.	F.	Cl.	Br.	I.	NO_2.
m	4·88	—	7·24	—	6·93	10·8
p	4·88	5·68	6·45	6·49	6·64	14·1

There is, however, an alternative, possible explanation of the k_2 values. For reasons already given, the mesomeric effect may be of little importance in the cyanohydrin so that the k_2 values might be influenced mainly by electron-attracting, electrostatic effects, inductive and inductomeric. Both these would be facilitating polar influences and hence a large inductomeric effect might be called into play in the transition state. Since the order of the inductive effect is $F > Cl > Br > I$, and that of the inductomeric is $I > Br > Cl > F$, their combined operation might well approximately equalise the overall electron-attracting power of the four halogens in the transition state and thus, in agreement with experiment, give rise to k_2 values of closely similar magnitudes. Moreover, the relative damping of the two effects in the *m*-position would probably be approximately the same so that both *m*- and *p*-values would be similar. The present experimental data do not permit any decision between these two explanations and more precise information regarding polarizability effects should accrue from the parallel study of the solvolysis of halogenobenzhydryl chlorides, to which reference has already been made.

Summarising the conclusions derived from this investigation, it is evident that the halogens exert strong inductive ($-I$) and mesomeric ($+M$) effects, both of which decrease in the order $F > Cl > Br > I$, and that there is considerable second-order relay of the $+M$ effect from the *m*-position. The results could be satisfactorily accounted for on the basis of these two polar influences alone if the $+M$ effect is modified (as indeed it must be) by the degree and extent of the unsaturation in the system to which it is attached. If an inductomeric effect is operative, it must be one of electron-*attraction*, which decreases in the reverse order $I > Br > Cl > F$. The magnitude of the $+M$ effect in the halogenobenzaldehydes would seem to preclude the incidence of any additional electromeric ($+E$) effect in the forward reaction (the only stage at which it might be called into play) and, in fact, the electron-release by this mechanism is smaller in the transition state than it is in the original aldehyde.

Discussion of Bird and Ingold's results (*loc. cit.*) for the nitration of the halogenobenzenes, where iodine and fluorine exhibit comparable electron-release effects, both greater than those

of chlorine and bromine, is best deferred until the results of the parallel series of investigations are available, but the present data do suggest that the polarizability electron-*release* effect responsible for *op*-orientation by the halogens may be inductomeric in character rather than electromeric, as was originally postulated by those authors.

Experimental.

Preparation of Materials.—m- *and* p-*Halogenobenzaldehydes.* Although in their initial preparation each aldehyde was found to require its own special method (see below), a standard method of purification was used. This consisted of converting the distilled aldehyde into its bisulphite compound from which, after washing with ether, the aldehyde was regenerated, steam-distilled, and converted into its semicarbazone. This derivative was purified by repeated crystallisation, usually from methyl alcohol, to a sharp, constant m. p. (standard rate of heating essential) and the aldehyde was regenerated from the pure semicarbazone by steam-distillation with aqueous oxalic acid in a current of carbon dioxide. The collected aldehyde was dried in ether solution and then carefully fractionated under reduced pressure (nitrogen), the fraction of constant b. p. being retained. Since both *m*- and *p*-iodobenzaldehyde tended to lose iodine during distillation they were finally purified by crystallisation from ligroin (b. p. 40—60°). All aldehydes were stored in small dark bottles under nitrogen and were freshly redistilled in nitrogen under reduced pressure (or recrystallised) immediately before use. The data given refer to the m. p. and b. p. of pure specimens of the aldehydes and their derivatives.

p-*Chlorobenzaldehyde.* Dry chlorine was passed into boiling, pure *p*-chlorotoluene (b. p. 66·5—67°/29 mm.) illuminated by a 150-watt lamp, and under a reflux condenser partly filled with small glass beads. Fractionation of the product gave *p*-chlorobenzyl chloride, b. p. 96—96·5°/14 mm., which was converted into the aldehyde by refluxing with an equimolecular weight of hexamethylenetetramine in aqueous alcohol for 2 hours in a current of carbon dioxide. After removal of the alcohol by distillation, the aldehyde was distilled in steam (carbon dioxide stream), extracted with ether, and converted directly into its bisulphite compound for purification: semicarbazone, m. p. 227°; *p*-chlorobenzaldehyde, b. p. 92°/16 mm., m. p. 48°.

p-*Bromobenzaldehyde.* Side-chain bromination of 128 g. of *p*-bromotoluene, b. p. 64—65°/14 mm. (from *p*-toluidine), with 120 g. of dry bromine was effected by a procedure similar to that described in *Org. Synth.* (Coll. Vol. 2, 89) with strong illumination and at 110° for the first hour, the temperature then being raised to 150° during the second hour. The resulting *p*-bromobenzyl bromide, b. p. 130—131°/16—17 mm., m. p. 61·5°, was converted into the aldehyde by the hexamine method; semicarbazone m. p. 226°; *p*-bromobenzaldehyde, b. p. 109°/16 mm., m. p. 58°.

p-*Iodobenzaldehyde.* Dry bromine (1 mol.) was added during 2 hours to 50—60 g. of *p*-iodotoluene, b. p. 89—90°/12 mm., at 140° but without illumination. Fractionation of the product gave *p*-iodobenzyl bromide, b. p. 115—120°/0·6 mm., m. p. 77—77·5°, which was converted into the aldehyde as before. The last traces of *p*-iodobenzyl bromide are retained in a considerable tarry residue and require stronger heating for their removal. The yield is very poor; semicarbazone, m. p. 224°; *p*-iodobenzaldehyde, b. p. 98°/1·4 mm., m. p. 76°.

p-*Fluorobenzaldehyde.* *p*-Fluorotoluene (Messrs. British Drug Houses, Ltd.) was chlorinated as described for *p*-chlorotoluene, but without illumination, until the b. p. of the liquid registered by a thermometer below the liquid surface reached 160°. Repeated fractionation of the product gave *p*-fluorobenzyl chloride, b. p. 70—71°/16 mm., for conversion into the aldehyde; b. p. 70°/20 mm.; semicarbazone, m. p. 216°.

m-*Chlorobenzaldehyde.* A purified sample of *m*-nitrobenzaldehyde, b. p. 146—147°/14 mm., was reduced to the amino-aldehyde with A. R. stannous chloride in hydrochloric acid (*Org. Synth.*, Vol. 13, 28) which was diazotised without isolation and converted by cuprous chloride into *m*-chlorobenzaldehyde, b. p. 90°/14 mm.; semicarbazone, m. p. 226°.

m-*Bromobenzaldehyde.* The method analogous to that used for the *m*-chloro-compound gave a product appreciably contaminated with *m*-chlorobenzaldehyde, which could not be removed by repeated crystallisation of its semicarbazone or by fractional distillation. *m*-Nitrobenzaldehyde was reduced with sodium dithionite at 80° (Hodgson and Beard, *J. Soc. Chem. Ind.*, 1926, **45**, 91T), the reduced solution was cooled, acidified with sulphuric acid, diazotised, and treated with a solution of cuprous bromide. The purified *m*-bromobenzaldehyde had b. p. 101°/11 mm.; semicarbazone, m. p. 225°.

m-*Iodobenzaldehyde.* The methods used for the *m*-bromo- and *m*-chloro-compounds proved unsuccessful when applied to the *m*-iodo-derivative. *m*-Iodotoluene, b. p. 96°/21 mm. (from *m*-toluidine), was brominated under the conditions used for *p*-iodotoluene except that a temperature of 180° was employed. The product fraction of b. p. 153—156°/12 mm. was purified by repeated crystallisation from ligroin (b. p. 40—60°) to give *m*-iodobenzyl bromide, m. p. 49—49·5°, which was converted by the hexamine method into *m*-iodobenzaldehyde, b. p. 124—125°/13 mm., m. p. 57°; semicarbazone, m. p. 224°.

m-*Fluorobenzaldehyde.* Chlorination of *m*-fluorotoluene under the conditions used for the *p*-compound gave a product, b. p. 152—156°/20 mm., with a blue fluorescence which was not *m*-fluorobenzyl chloride. Chlorination was successfully effected when carried out with strong illumination by a 500-watt lamp. Repeated fractionation of the main fraction gave *m*-fluorobenzyl chloride, b. p. 69·5—72·5°/21 mm. This was converted as usual into *m*-fluorobenzaldehyde, b. p. 67°/19 mm.; semicarbazone, m. p. 212·5°.

Benzaldehyde. An " extra pure " specimen (Messrs. British Drug Houses, Ltd.) was put through the usual purification, the sample used having b. p. 74°/24 mm.

m-*Nitrobenzaldehyde.* A purchased sample was steam distilled to remove a yellow pigment, and converted into its semicarbazone which was crystallised from glacial acetic acid; m. p. 246°. The aldehyde was regenerated by steam-distillation with 50% sulphuric acid and purified by repeated crystallisation from ligroin (b. p. 40—60°) to give a sample, m. p. 56·5°.

p-*Nitrobenzaldehyde.* This was best purified by sublimation under reduced pressure (17 mm.), followed by repeated crystallisation from carbon tetrachloride, to give a specimen, m. p. 104·5—105°.

Liquid hydrogen cyanide from a cylinder, kindly supplied by Messrs. Imperial Chemical Industries Ltd., was carefully distilled from phosphoric oxide in an all-glass apparatus fitted with an anti-splash head. The stock solution was prepared by dissolving 16 ml. of the pure distillate in 400 ml. of constant-b. p. alcohol to give an approximately M-solution, which was stored in dark bottles with well-ground glass stoppers sealed with paraffin wax.

The constant-boiling alcohol solvent, catalysts, and standard solutions were prepared, and apparatus calibrated, as described by Baker and Hemming (*loc. cit.*).

Equilibria and Velocity Determinations.—These were carried out by means of the microtechnique described by Baker and Hemming in thermostats controlled to 20° ± 0·02°. The consistency of the determinations is shown by the following summary of the results of individual experiments, from which the final mean data in Table I were obtained.

Summary of experimental data for the reaction

$$X\cdot C_6H_4\cdot CHO + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X\cdot C_6H_4\cdot CH(OH)\cdot CN$$

in constant-b. p. alcohol at 20° ± 0·02°.

Velocity catalyst = 0·01M-pyridine + 0·01M-pyridinium benzoate.
Equilibrium ,, = 2 drops (~0·02 g.) of NPr_3 per 50 ml.

X.	Individual values of 10^3K, g.-mol. l.$^{-1}$.	Mean 10^3K.	Individual values of 10^3k_1, g.-mol.$^{-1}$ l. sec.$^{-1}$.	Mean 10^3k_1.
H	4·53, 4·67, 4·27, 4·23, 4·44, 4·37, 4·66, 4·39	4·45 ± 0·13 *	1·63, 1·66	1·65 ± 0·02
p-F	6·44, 6·33, 6·44, 6·11, 6·10, 6·40 †	6·30 ± 0·13	3·60, 3·59	3·59 ± 0·01
p-Cl	3·90, 3·62, 4·02, 3·86	3·85 ± 0·12	6·98, 6·90	6·94 ± 0·04
p-Br	3·26, 3·31, 3·17, 3·31	3·26 ± 0·05	9·07, 9·20	9·14 ± 0·07
p-I	3·18, 3·08, 3·12	3·13 ± 0·04	9·29, 9·46	9·38 ± 0·09
m-F	2·11, 2·16, 2·11	2·13 ± 0·02	10·20, 10·23	10·22 ± 0·02
m-Cl	1·95, 1·97, 1·98	1·97 ± 0·01	12·43, 12·47	12·45 ± 0·02
m-Br	1·90, 1·86	1·88 ± 0·02	14·16, 14·48	14·32 ± 0·16
m-I	2·08, 2·03, 1·96	2·02 ± 0·04	14·01, 14·97, 14·47	14·5 ± 0·3

* Mean deviation from the mean value.
† From a " velocity " experiment allowed to attain equilibrium.

m- and *p*-*Nitrobenzaldehydes.*—The upward drift in the hydrogen cyanide concentration, subsequent to reaching its minimum value, when the catalyst used was one drop of tri-*n*-propylamine, is illustrated by the following calculated values of the " equilibrium " constant at progressive time intervals from the commencement of the experiments.

m- 10^3K	(1) 3·70. (2) 4·20. *ca.* 3				(1) 5·16. (2) 6·00. *ca.* 24			
m- Time, hrs.								
p- 10^3K	12·5	10·0	7·4	7·94	11·3	15·7	26·5	34·3
p- Time, hrs.	0·67	1·17	2·67	4·67	22·0	29·75	50·67	68·17

With 0·01M-pyridine + 0·01M-pyridinium benzoate as catalyst, the corresponding drift is shown in the following table, which records the number of ml. (y) of 0·05N-ammonium thiocyanate required for the excess of 0·05N-silver nitrate after addition of 10 ml. of the silver nitrate to a 2-ml. sample of the reaction mixture :

m-NO_2	y, ml.	9·10	9·11	9·11, 9·12					whence 10^3K = 2·10 g.-mol. l.$^{-1}$.
	Time, hrs.	24	46	100					
p-NO_2	y, ml.	7·94	8·05	8·16	*8·86*	8·80	8·76	8·64	8·27	8·16
	Time, hrs.	6·80	7·58	8·23	24	32	54	72	125	150

Extrapolation to zero time of the straight line obtained by plotting the values of y against time over the period 24—150 hrs. gave an estimated value of $y_{max.}$ = 9·07 ml., whence 10^3K = 3·4 g.-mol. l^{-1}.

One of us (H. B. H.) wishes to thank the Research Fund of the Chemical Society for a grant.

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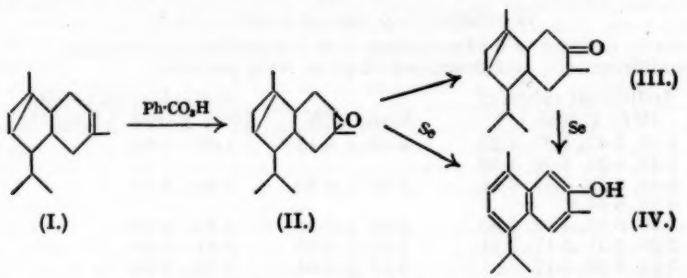
233. *The Constitution of Some Cadalene Derivatives.*

By L. H. Briggs, (Miss) Naida S. Gill, F. Lions, and W. I. Taylor.

The constitution of a number of monosubstitution products of cadalene, previously believed by Gripenberg to be 2-derivatives, has been confirmed by relating them to the known 1 : 2 : 6-trimethyl-4-*iso*propylnaphthalene. A synthesis of 7-hydroxy-1 : 6-dimethyl-4-*iso*propylnaphthalene (7-hydroxycadalene) has shown it to be identical with a product from copæne and supports the constitution of the latter recently proposed by two of us (L. H. B. and W. I. T.). A compound alleged by Gripenberg to have the same constitution must now be assigned some other, still unknown structure.

In experiments on the constitution of copæne (I) (Briggs and Taylor, *J.*, 1947, 1338) a phenolic compound, $C_{15}H_{18}O$, was isolated which, it was suggested, was probably the previously unknown 7-hydroxy-1 : 6-dimethyl-4-*iso*propylnaphthalene (7-hydroxycadalene) (IV) arising from the dehydrogenation of copæne oxide (II) or its isomeric ketone (III).



However, in an earlier publication (*Ann. Acad. Sci. Fennicæ, Ser. A*, 1943, **59**, No. 41), which appeared in abstract form only after this work was completed, Gripenberg described a compound arising from the alkali fusion of a cadalene sulphonic acid which, he suggested, had the structure (IV). Gripenberg also described a number of monosubstitution products of cadalene alleged to have the 2-configuration, including the 2-hydroxy-compound. The isomeric 5-hydroxycadalene is also known, having been synthesised by Plattner and Magyar (*Helv. Chim. Acta*, 1941, **24**, 191) by an unambiguous route. The phenolic compound from copæne, however, appeared not to be identical with any of these substances.

The structures for Gripenberg's 2- and 7-hydroxy-isomers were, however, based solely on inductive reasoning, and, although we concur completely with his deductions even to the structure of his alleged 7-hydroxy-isomer, we felt a more rigid proof of the configuration of his compounds to be necessary in elucidating the structure of the copæne by-product.

We have concluded the proof of the 2-substituted compounds of cadalene through the *chloromethyl* derivative obtained by direct chloromethylation of cadalene. Oxidation, on the one hand, *via* the *aldehyde*, affords a cadalenecarboxylic acid, identical with that obtained by Gripenberg from both bromocadalene and acetylcadalene (these products being obtained from cadalene by direct bromination and the action of acetyl chloride in the Friedel and Crafts reaction, respectively) and having the suggested 2-configuration. Reduction, on the other hand, gave the 1 : 2 : 6-trimethyl-4-*iso*propylnaphthalene which was synthesised by Campbell and Soffer (*J. Amer. Chem. Soc.*, 1942, **64**, 417) by an unambiguous method. Since the 2-hydroxy-isomer of cadalene can be directly related to the above bromo- and acetyl derivatives (*q.v.*) its structure is confirmed.*

We attempted to establish the structure of the alleged 7-hydroxy-derivatives first from cadalene itself. We have prepared cadalenesulphonic acid and from it the corresponding naphthol and confirmed their properties given by Gripenberg. The naphthol considerably depresses the melting point of the copæne isomer, thus eliminating the possibility of their being dimorphic forms.

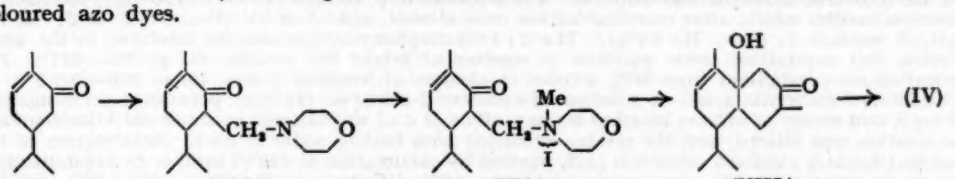
Oxidation of the sulphonic acid with permanganate should ultimately break the ring to which the sulphonic acid group is not attached, but the only product isolated from an experiment designed for this purpose was trimellitic acid in very small yield. As the corresponding

* Since this work has been completed, Dr. Gripenberg has informed us that he had already, in unpublished work, proved the configuration of the 2-derivatives by converting the bromo-derivative *via* its Grignard compound and orthoformic ester into the corresponding aldehyde, reduction of which gave 1 : 2 : 6-trimethyl-4-*iso*propylnaphthalene.

sulphonamide should behave similarly and the products should be easier to characterise, the corresponding sulphonamide was oxidised in a similar manner; it afforded, in small yield, (*a*) a viscous, liquid acid, giving a liquid methyl ester, and (*b*) a solid acid, $C_{15}H_{17}O_4NS$, characterised as its solid methyl ester and containing a sulphonamide group and all the original carbon atoms, one of which is oxidised to carboxyl. The liquid acid could correspond in properties to 4-sulphonamidotrimellitic acid (Jacobsen, *Ber.*, 1883, **16**, 192), but the solid acid is new and throws no light on the problem.

It seemed at this point that a simpler approach might be made synthetically, and 7-hydroxycadalene has now been synthesised unequivocally by the following series of reactions.

Carvotanacetone (V) was converted by paraformaldehyde and morpholine hydrochloride into the Mannich base (VI) (probably a mixture of stereoisomers), and the methiodide (VII) was condensed with ethyl sodio-α-acetylpropionate in absolute alcohol. Hydrolysis with potassium hydroxide solution then afforded 9-hydroxy-7-keto-1 : 6-dimethyl-4-*iso*propyl-Δ^1-octalin (VIII). Although hydroxy-ketones are usually dehydrated under such experimental conditions, Mannich, Koch, and Borkowsky (*Ber.*, 1937, **70**, *B*, 355) isolated a similar compound in their synthesis of β-octalone. Dehydration, reduction, and dehydrogenation of the hydroxy-ketone was achieved in one step by heating it with palladised charcoal in boiling diphenyl ether (cf. Horning and Horning, *J. Amer. Chem. Soc.*, 1947, **69**, 1360). The resultant 7-hydroxy-1 : 6-dimethyl-4-*iso*propylnaphthalene (7-hydroxycadalene) (IV), m. p. 119°, was characterised as the picrate and trinitrobenzene compound and shown by direct comparison to be identical with the naphthol from copæne, m. p. 116°, thus confirming the structure of copæne proposed by two of us (L. H. B. and W. I. T.). It couples with diazotised amines in alkaline solution to form dark-coloured azo dyes.



(V.) (VI.) (VII.) (VIII.)

Gripenberg's " 7-hydroxy "-isomer must therefore have some other structure. Sulphonation of naphthalene derivatives at 135°, as in his experiment, usually affords a β-sulphonic acid, in this case theoretically the 2-, 3-, or 7-derivative. That the acid occupies a β-position is shown by the fact that it is unchanged by attempted reduction with sodium amalgam, a diagnostic test introduced by Friedlaender and Lucht (*Ber.*, 1893, **26**, 3028) who showed that α-sulphonic acids, unlike the β-acids, are hydrolysed by this reagent. The 2- and 7-isomers may now be eliminated from the experiments described above. The 3-isomer, however, is unlikely since sulphonation usually proceeds in the less alkylated ring and also because the corresponding naphthol with no free adjacent α-position should not couple with diazotised amines, which it does. Possibly, in this case, wandering of an alkyl group occurs. This is common in heavily alkylated benzene and naphthalene derivatives, although it would not normally be expected in this case.

Experimental.

Preparation of Cadalene.—Crude cadinene (250 g., b. p. 120—140°/10 mm.), obtained by the distillation of oil of cade, was dehydrogenated with selenium (220 g.) for 70 hours at 300°. The crude cadalene fraction (120 g., b. p. 140—160°/10 mm.) was converted into the picrate, which was purified by crystallisation from alcohol to a constant m. p. 116—117° (yield 85 g.). The hydrocarbon was regenerated by decomposition with aqueous ammonia and extraction with ether, from which distillation afforded pure cadalene, b. p. 155—158°/10 mm.

Bromination of Cadalene.—To ice-cold cadalene (4·13 g.) in carbon tetrachloride (5 c.c.) ice-cold bromine (2·48 g.) in the same solvent (4 c.c.) was slowly added. After being kept for a day the solution was washed with alkali and water, and dried (Na_2SO_4), and the solvent was removed. Distillation then afforded crude 2-bromocadalene, b. p. 170—172°/8 mm. (4·3 g.). After it had been kept for some days in the refrigerator, pure 2-bromocadalene crystallised in plates, which after recrystallisation from methyl alcohol and alcohol had m. p. 39° (Found : Br, 28·4. Calc. for $C_{15}H_{17}Br$: Br, 28·9%). We could not confirm the m. p. 52—52·5° given to this compound by Gripenberg. The picrate, long orange needles, m. p. 114—115°, from alcohol, and the trinitrobenzene complex, yellow needles, m. p. 125—126°, from absolute alcohol, agreed in properties with those of Gripenberg (m. p. 113—113·5° and 124·5—125° respectively). The trinitrotoluene complex crystallised well, from methyl alcohol, in yellow needles, m. p. 87°.

The residue from the distillation of 2-bromocadalene was extracted with boiling alcohol (charcoal)

and yielded a small quantity of a dibromocadalene, needles, m. p. 121—122° (Found: Br, 44·6. $C_{15}H_{16}Br_2$ requires Br, 44·9%), which failed to yield derivatives with picric acid and trinitrobenzene.

When an attempt was made to convert 2-bromocadalene into the 2-methyl derivative *via* the Grignard product and methyl sulphate, cadalene (trinitrobenzoate, m. p. and mixed m. p. 113°) was the only product isolated.

Chloromethylation of Cadalene.—Cadalene (3 g.), paraformaldehyde (1 g.), glacial acetic acid (4·5 c.c.), concentrated hydrochloric acid (5 c.c.), and syrupy phosphoric acid (0·85 c.c.) were vigorously stirred at 100° for 6 hours. After dilution with water (30 c.c.), the product yielded to ether after washing (dilute sodium hydroxide solution) and drying (Na_2SO_4) an oil giving the following fractions on distillation: (*a*) solid, m. p. 84°, b. p. 100—180°/10 mm., 1·5 g., (*b*) semi-solid, b. p. 180—230°/10 mm., 0·34 g., and (*c*) solid, m. p. 154—156°, b. p. *ca.* 230/0·01 mm., 0·85 g. Fraction (*a*), *2-chloromethylcadalene*, crystallised readily from alcohol, in aggregates of small needles, m. p. 87° (Found: C, 77·7; H, 7·8. $C_{16}H_{19}Cl$ requires C, 77·9; H, 7·8).

The picrate was unstable, but the *trinitrobenzene* complex crystallised from absolute alcohol in yellow needles, m. p. 91—92° (Found: N, 9·7. $C_{16}H_{19}Cl,C_6H_3O_6N_3$ requires N, 9·2%).

Fraction (*c*), *2 : 2′-dicadalylmethane*, almost insoluble in boiling alcohol, methyl alcohol, and acetone, crystallised from glacial acetic acid in stout rods, m. p. 154—156° (Found: C, 91·2; H, 9·2. $C_{31}H_{36}$ requires C, 91·1; H, 8·9%). The picrate formed from the hydrocarbon (1 mol.) and picric acid (2 mols.) crystallised from glacial acetic acid in stout rods, m. p. 124—126°, but decomposed in alcohol and benzene.

When 2-chloromethylcadalene was chloromethylated as described above, besides unchanged material, a small yield (35 mg. from 500 mg.) of a *bischloromethylcadalene* was obtained which, after repeated crystallisation from alcohol, formed needles, m. p. 139—140° (Found: Cl, 22·6. $C_{17}H_{20}Cl_2$ requires Cl, 23·0%), and failed to yield a picrate or trinitrobenzene complex.

Cadalene-2-aldehyde.—2-Chloromethylcadalene (650 mg.) and hexamine (350 mg.) in alcohol (7 c.c.) were heated under reflux for 6 hours. The solution was diluted with water (10 c.c.), the alcohol removed by distillation, and the aqueous solution treated with saturated sodium hydrogen sulphite solution. The solid bisulphite compound, which formed in a few minutes, was washed with a little water and alcohol, and the recovered aldehyde was distilled. The fraction, b. p. *ca.* 120°/10 mm. (120 mg.), solidified in colourless needles which, after recrystallisation from alcohol, melted at 84° (Found: C, 84·2; H, 7·9. $C_{16}H_{18}O$ requires C, 84·9; H, 8·0%). The 2 : 4-dinitrophenylhydrazone was insoluble in the usual solvents, but crystallised from pyridine in rosettes of bright red needles, m. p. 270—271°. The semicarbazone crystallised from 80% alcohol in clusters of irregular plates, m. p. 206—207·5°.

Cadalene-2-carboxylic acid.—A solution of cadalene-2-aldehyde (34 mg.), potassium permanganate (16 mg.), and excess of sodium bicarbonate in acetone (3 c.c.) was allowed to stand until decolourised. The solution was filtered, and the residue extracted with boiling water (1 c.c.). Acidification of the combined filtrates yielded a colourless acid, purified by sublimation at 180°/1 mm. or by crystallisation from glacial acetic acid. The final product had m. p. 193°, slightly lower than that (195—196°) recorded by Gripenberg (Found: C, 79·5; H, 7·3. Calc. for $C_{16}H_{18}O_2$: C, 79·3; H, 7·5%).

1 : 2 : 6-*Trimethyl*-4-iso*propylnaphthalene.*—2-Chloromethylcadalene (230 mg.) and zinc (300 mg.) in glacial acetic acid (10 c.c.) were heated on the water-bath and saturated with hydrogen chloride. The acetic acid was removed by vacuum-distillation; the residue after extraction with ether yielded an oil, b. p. *ca.* 160°/10 mm. (60 mg.), the picrate and trinitrobenzene complex of which formed red needles, m. p. 142°, from alcohol, and yellow needles, m. p. 167°, from absolute alcohol, respectively, m. p.s which agree with those recorded by Campbell and Soffer (*J. Amer. Chem. Soc.*, 1942, **64**, 417) for the derivatives of 2-methylcadalene.

Cadalenesulphonic acid was prepared at 100° by a method similar to that described by Gripenberg, the free acid crystallising in plates from benzene, m. p. 121—122° (Gripenberg records m. p. 124—125°). The 5-benzyl-ψ-thiouronium salt had m. p. 228° after repeated crystallisation from alcohol (Gripenberg recorded m. p. 222—223°).

Cadalenesulphonamide.—Sodium cadalenesulphonate (500 mg.) and phosphorus pentachloride (600 mg.) were heated at 100° for 45 minutes. After cooling, the melt was triturated with water, and the crude sulphonyl chloride then heated under reflux with concentrated ammonia (20 c.c.) for 1½ hours. The sulphonamide produced, after crystallisation from alcohol, formed colourless needles, m. p. 157—158°, unchanged by further recrystallisation (Found: N, 4·8. Calc. for $C_{15}H_{19}O_2NS$: N, 5·05%). We could not confirm the m. p. 175·5—176° given to this compound by Gripenberg.

The Hydroxycadalene from Cadalenesulphonic Acid.—Sodium cadalenesulphonate (600 mg.) was fused with potassium hydroxide (1 g.) at 310° for 35 minutes with continuous stirring. After cooling, the melt was dissolved in water, acidified, and extracted with ether. After being washed with sodium bicarbonate solution and dried (Na_2SO_4), the extract yielded a viscous red oil, b. p. *ca.* 200°/10 mm. (150 mg.), which partly solidified when kept in the refrigerator. Crystallisation from 50% alcohol gave the pure hydroxycadalene, m. p. 89°, corresponding to the product, m. p. 90°, described by Gripenberg. The m. p. was depressed to 74° after admixture with a specimen of 7-hydroxycadalene, m. p. 116°, derived from copæne.

Oxidation of Cadalenesulphonic Acid.—Potassium permanganate (27 g.; 26 atoms of oxygen) was slowly added to potassium cadalenesulphonate (4·0 g., 1 mol.) in water (200 c.c.). After a rapid initial oxidation, the mixture was heated on the water-bath for 3 days. Manganese dioxide was then filtered off, and lead acetate (25 c.c. of a 25% solution) added to the filtrate acidified with acetic acid. After concentration of the solution to *ca.* 50 c.c., a solid crystallised out in rods (yield, *ca.* 1 g.). This was suspended in water, saturated with hydrogen sulphide, and filtered; the solution, when evaporated to dryness, gave a white solid, freely soluble in water. Fusion of this product with potassium hydroxide at 160—170° for 15 minutes and working up in the usual way failed to give a phenolic product. However, extraction, with ether, of the original oxidation mother-liquors yielded trimellitic acid (15 mg.), m. p. 210—216°, characterised by its anhydride, m. p. 158°, which was undepressed by an authentic specimen prepared from ψ-cumene.

Oxidation of Cadalenesulphonamide.—A mixture of cadalenesulphonamide (3·68 g.), potassium permanganate (21 g., 24 atoms of oxygen), and potassium carbonate (6 g.) in acetone (150 c.c.) was heated under reflux for 24 hours. The acetone-insoluble portion was extracted with boiling water (100 c.c.), and this on acidification with dilute sulphuric acid gave a sticky solid (*A*), whilst exhaustive extraction with ether afforded a further quantity of oily material (*B*).

(*A*) was dissolved in dilute sodium carbonate solution, any neutral component extracted with ether, and the solution acidified. A semi-solid mixture of acids was obtained, separated by crystallisation from alcohol into needles (69 mg.) and an oil (200 mg.). The crystalline *acid* had m. p. 254—255° (Found: C, 58·5; H, 5·3; N, 4·6. $C_{15}H_{17}O_4NS$ requires C, 58·6; H, 5·6; N, 4·6%) and with diazomethane furnished a methyl ester, m. p. 157—158°. The solid acid exhibits a purple fluorescence in alcohol. The oil was dissolved in dry acetone, chromatographed on charcoal, and eluted with the same solvent. The major part of the eluate furnished an oil, but the final fractions yielded a further 35 mg. of the above acid.

Similar chromatography of (*B*) and elution failed to yield a solid product, whilst a methyl ester prepared by the action of diazomethane, although semi-solid, could not be induced to crystallise.

Synthesis of 7-Hydroxycadalene.—(a) *3-Morpholinomethylcarvotanacetone methiodide.* A mixture of carvotanacetone (25·4 g., 1/6 mol.), morpholine hydrochloride (21·7 g., 1/6 mol.), paraformaldehyde (1·7 g.), and absolute alcohol (30 c.c.) was heated under reflux. At the end of each half-hour, further additions of paraformaldehyde (1·7 g.) were made until a total of 6·8 g. had been added, and the boiling was continued for 4 hours in all; the mixture was then homogeneous. As no crystalline hydrochloride separated after cooling the mixture, some of the alcohol was removed and the residue diluted with water. Unchanged ketone was removed with ether, and the free Mannich base liberated from the aqueous solution by treatment with ice-cold sodium hydroxide solution (8 g. in 25 c.c.). The free base was obtained as a dark oil (30 g.) by extraction with ether. Methyl iodide (28 g., 20% excess) was added to a solution of the base (41 g.) in dry ether, and the mixture set aside overnight. The methiodide separated as a brownish-yellow gum (58 g.) which, however, could not be induced to crystallise.

(b) *9-Hydroxy-7-keto-1 : 6-dimethyl-4-isopropyl-Δ^1-octalin.* A solution of ethyl sodio-α-acetylpropionate was prepared from ethyl α-acetylpropionate (31·3 g.) and sodium (5·1 g.) in absolute alcohol (130 c.c.). The solution was then added to the methiodide (57 g.), dissolved in dry alcohol, which was possible with mechanical shaking if the methiodide had not been allowed to stand too long. Otherwise, it was added to the methiodide, and the mixture gently warmed in an oil-bath, with shaking, until the gum left the walls of the flask. The mixture was then heated under reflux for 5 hours. In order to hydrolyse the ester so formed, potassium hydroxide solution (9 g. in 20 c.c.) was added, and the heating under reflux continued for a further 4 hours. Most of the alcohol was then distilled off, and sufficient water added to dissolve the sodium iodide formed in the reaction and to cause the oily product to separate. The oil, removed by ether extraction, furnished *9-hydroxy-7-keto-1 : 6-dimethyl-4-isopropyl-Δ^1-octalin* as a yellow oil, b. p. 150—154°/1—2 mm. (yield 16·1 g.) (Found: C, 74·9; H, 9·7. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). The *2 : 4-dinitrophenylhydrazone* crystallised from alcohol in orange needles, m. p. 167° (Found: N, 13·4. $C_{21}H_{28}O_5N_4$ requires N, 13·5%). The *semicarbazone* crystallised from alcohol in colourless needles, m. p. 208·5° (Found: N, 14·3. $C_{16}H_{27}O_2N_3$ requires N, 14·3%).

(c) *7-Hydroxycadalene.* Palladium–charcoal catalyst (1·5 g.) was added to 9-hydroxy-7-keto-1 : 6-dimethyl-4-*iso*propyl-Δ^1-octalin (5 g.) in diphenyl ether (15 c.c.), and the mixture heated at *ca.* 270° for 2 hours. After removal of the catalyst, the naphthol was extracted with Claisen solution according to the method of Horning and Horning (*J. Amer. Chem. Soc.*, 1947, **69**, 1360). After acidification of the alkaline extract with concentrated hydrochloric acid, the product was removed with ether and distilled. The viscous oil obtained, b. p. 172°/1 mm. (bath-temperature, 300°), solidified when scratched. Recrystallisation from light petroleum (b. p. below 60°) yielded colourless needles, m. p. 119°, undepressed on admixture with the naphthol from copæne (Found: C, 83·2; H, 8·6. Calc. for $C_{15}H_{18}O$: C, 84·1; H, 8·5%). The picrate formed reddish-brown needles, m. p. 138°, and decomposed on long storage; the trinitrobenzene complex crystallised from alcohol in orange-red needles, m. p. 140—140·5°. Neither product depressed the m. p. (139° and 139—140°, respectively) of the corresponding derivatives from the copæne naphthol.

The analyses are by Drs. Weiler and Strauss, Oxford, and Miss J. E. Fildes, University of Sydney.

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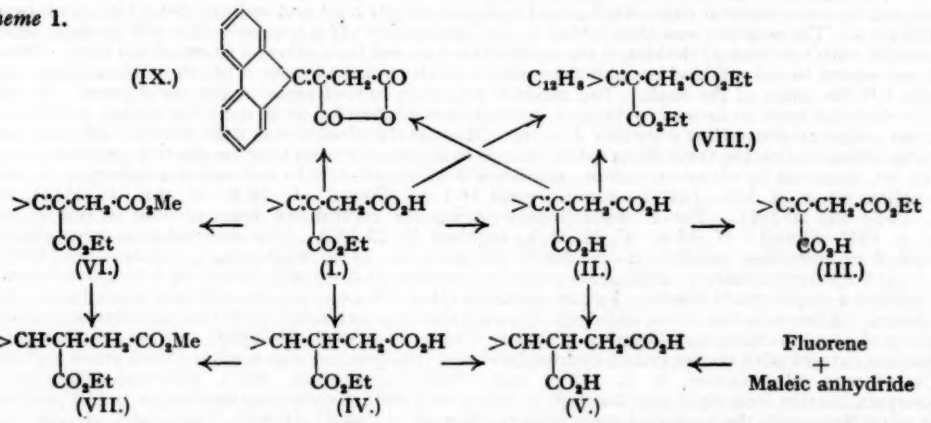
234. *The Condensation of Fluorenone and Ethyl Succinate.*

By Neil Campbell and A. E. S. Fairfull.

Fluorenone and ethyl succinate condense in presence of potassium *tert.*-butoxide or sodium hydride to give a mixture from which *β-carbethoxy-β-fluorenylidenepropionic acid* (I) and 1 : 4-*difluorenylidenesuccinic acid* (XIX) have been isolated. With sodium ethoxide only the latter was isolated. The chemistry of the former product and its derivatives has been investigated, and the inability of the latter to form an anhydride explained on stereochemical grounds.

The synthetic value of 3 : 3-disubstituted itaconic acids (Borsche, *Annalen*, 1936, **526**, 1; Cook and Preston, *J.*, 1944, **553**, etc.) led us to prepare and study *fluorenylidenesuccinic acid* (3 : 3-*diphenylenecitraconic acid*). We first attempted to prepare the compound by condensing fluorenone with ethyl succinate by means of sodium ethoxide (Stobbe, *Annalen*, 1899, **308**, 89), but later adopted the procedure of Johnson and his co-workers (*J. Amer. Chem. Soc.*, 1945, **67**, 1357, 1360, 1366) in which potassium *tert.*-butoxide is used. By the latter method a mixture of products was obtained the nature of which was not completely elucidated (see below), but we isolated *β-carbethoxy-β-fluorenylidenepropionic acid* (I), referred to below as the "half-ester." Its constitution was suggested by the formation of the analogous ester from benzophenone and ethyl succinate (Stobbe, *Annalen*, 1894, **282**, 281; 1899, **308**, 98; Borsche, *loc. cit.*; Johnson *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 74) and confirmed by the reactions shown in scheme 1.

Scheme 1.



Thus, in particular, the carbon skeleton was proved by formation, in several steps, of *9-fluorenylsuccinic acid* (V), which was prepared also from fluorene and maleic anhydride; the sterically hindered position of the esterified carboxyl group was proved by formation of the isomeric *monoethyl* ester (III), rather than the original ester, on esterification of the *dicarboxylic acid* (II); and the presence of the methylene group in the unsaturated compounds is shown by condensation of the *diester* (VIII) with benzaldehyde to give α-benzylidene-α′-9-fluorenylidenesuccinic acid, which is also obtained from fluorenone and ethyl phenylitaconate (Stobbe *et al.*, *Annalen*, 1911, **380**, 126). The structure of the isomeric monoethyl ester (III) is also proved by similar reactions.

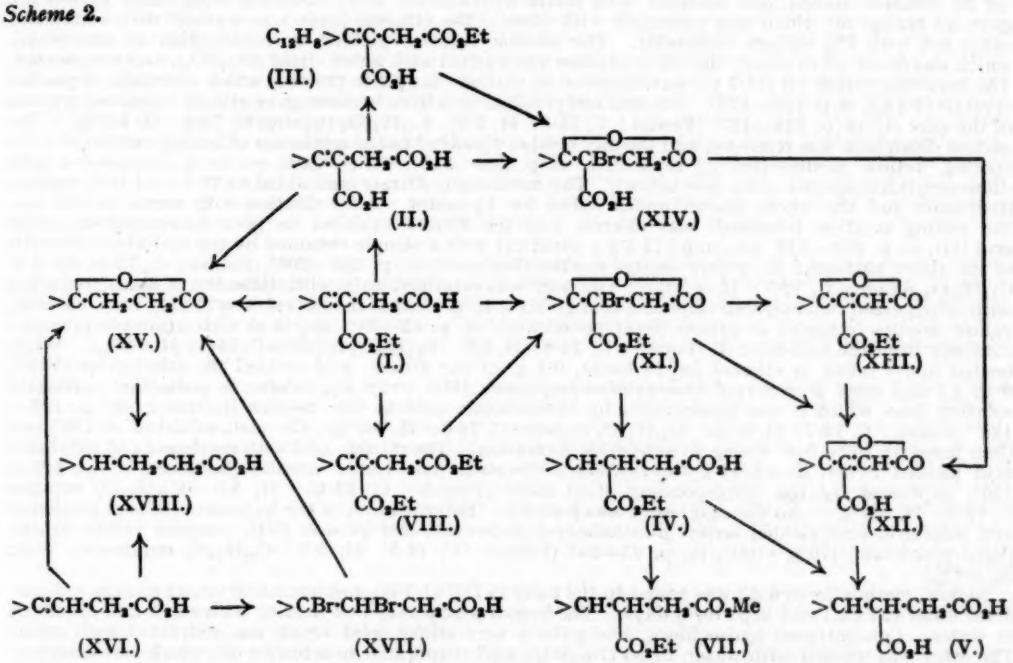
Interaction of the diacid and its esters with bromine leads to *bromo-lactones* (XI) and (XIV) (see scheme 2), formed by elimination of hydrogen bromide between CO_2H and $\geqslant$CBr or of ethyl bromide between CO_2Et and $\geqslant$CBr (cf. Stobbe, *Ber.*, 1911, **44**, 1297).

The acid (I) with hydrobromic acid and acetic acid (cf. Johnson, *loc. cit.*) was hydrolysed and decarboxylated to the *lactone* (XV), also prepared in the same way from the acid (II) or from β-fluorenylidenepropionic acid (XVI) either by sulphuric acid or *via* its *dibromo*-derivative (XVII). The lactone was reduced by hydriodic acid and red phosphorus to β-9-fluorenylpropionic acid (XVIII), also obtained by reduction of the acid (XVI).

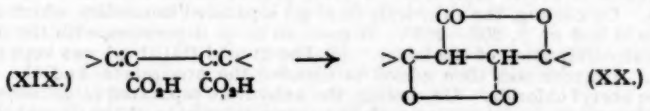
Attempts at ring-closure by refluxing the half-ester (I) with sodium acetate and acetic anhydride or by treating the dibasic acid (II) with concentrated sulphuric acid or aluminium chloride in nitrobenzene (cf. Stobbe and Gollücke, *Ber.*, 1906, **39**, 1066) were unsuccessful. Failure to form an indone derivative with two contiguous five-membered rings in an aromatic system is not surprising, but failure to obtain a fluoranthene derivative was unexpected in view

of Borsche's conversion (*loc. cit.*) of 2-carbethoxy-3 : 3-diphenylvinylacetic acid into a derivative of phenylnaphthol.

Scheme 2.



In the Stobbe condensations with sodium ethoxide a yellow product was obtained; it was also formed in the Johnson modification at the expense of the half-ester (I) when heating lasted for more than 30 minutes. A molecular-weight determination indicated that two molecules of fluorenone had condensed with one of ethyl succinate, and analysis supported the belief that the yellow compound was *difluorenylidenesuccinic acid* (XIX). This was confirmed by decarboxylation to *difluorenylidene-ethane* followed by reduction to di-9-fluorenylethane.



It was found that fluorenone and ethyl succinate with sodium hydride gave the same products as with potassium *tert.*-butoxide.

The dicarboxylic acid (XIX) when heated under reflux with acetic acid and hydrobromic acid gave a *dilactone* (XX), but all efforts to prepare the anhydride failed. This is most plausibly attributed to the *trans*-configuration of the carboxyl groups which involves slight overlapping of the fluorene residues and carboxyl groups, while the *cis*-configuration required for anhydride formation would result in heavy overlapping of the fluorene nuclei. Stobbe *et al.* (*loc. cit.*) obtained the anhydride from α-phenyl-β-diphenylenefulgenic acid only on long boiling with acetyl chloride. It is noteworthy that Koelsch and Richter (*J. Org. Chem.*, 1939, **3**, 473) easily obtained the anhydride of tetraphenylfulgenic acid. This striking difference between molecules very similar in structure is probably to be explained by the rigidity of the fluorene molecule which causes the whole molecule to be coplanar or nearly so, while in the tetraphenylfulgenic acid the phenyl rings are not necessarily coplanar and consequently the *trans*-acid can be converted into the *cis*-acid by the blocking phenyl groups tilting and then " sliding past " one another.

Experimental.

Aluminium oxide (Brockmann) was used for the chromatographic adsorption experiments, and a Hanovia ultra-violet lamp for the fluorescence observations. The identity of different samples was established by mixed m. p.s, and analyses were by Drs. Weiler and Strauss, Oxford.

β-Carbethoxy-β-fluorenylidenepropionic Acid (I).—Fluorenone (9 g., 0·05 mol.) in ethyl succinate (13·05 g., 0·075 mol.) and *tert.*-butanol (30 ml.) were cooled to 0° and added to a chilled solution of potassium (2·15 g., 0·055 mol.) in *tert.*-butanol (45 ml.). The solution was gently heated under reflux for 35 minutes, cooled, and acidified with dilute hydrochloric acid. Dilution with water to 600 ml. gave an orange oil which was extracted with ether; the ethereal layer was washed with water and extracted with 5% sodium hydroxide. The alkaline solution yielded on acidification an orange oil, which was dissolved in ether; the ether solution was washed with water, dried (Na_2SO_4), and evaporated. The resulting yellow oil (11·7 g.) was dissolved in carbon disulphide (20 ml.) which overnight deposited crystals (4·4 g.), m. p. 120—123°. Several recrystallisations from benzene gave almost colourless crystals of the *ester* (I), m. p. 126—127° (Found: C, 73·6; H, 5·3. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%). The carbon disulphide was removed, and the oily residue dissolved in the minimum of boiling methanol. On cooling, yellow needles (0·6 g.) separated, m. p. 208—210°, which gave no m. p. depression with difluorenylidenesuccinic acid (see below). The methanolic filtrate was added to 75 c.c. of 10% sodium hydroxide and the whole heated under reflux for 1½ hours. After dilution with water to 150 c.c., the boiling solution (charcoal) was filtered, and the filtrate acidified to give *fluorenylidenesuccinic acid* (II), m. p. 202—204° (decomp.) (3·3 g.), identical with a sample obtained by the hydrolysis (NaOH) of the above half-ester (I), yellow-orange needles (benzene), m. p. 205—206° (Found: C, 72·9; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%). The acid was esterified only with difficulty, 4 hours' refluxing with ethanol and concentrated sulphuric acid giving a 15% yield of the *diethyl* ester (VIII), m. p. 83—84°, yellow needles (ethanol) or prisms (light petroleum), m. p. 83—84°, identical with a sample prepared similarly from the half-ester (I) (Found: C, 74·8; H, 5·9. $C_{21}H_{20}O_4$ requires C, 75·0; H, 6·0%). When heated under reflux in ethanol for 24 hours, 0·5 g. of the dibasic acid yielded the ethyl ester (VIII; 0·12 g.) and *ethyl β-carboxy-β-fluorenylidenepropionate* (III) (0·28 g.), soluble in potassium carbonate solution from which it was precipitated by hydrochloric acid as fine needles (benzene), m. p. 127—128° (Found: C, 73·7; H, 5·15. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%); the melt solidified at 170° and then fused at 202—204° owing to anhydride formation. The dibasic acid with methanol and sulphuric acid yielded *methyl β-carboxy-β-fluorenylidenepropionate*, pale yellow needles (benzene), m. p. 125—126°, depressed by the corresponding ethyl ester (Found: C, 73·45; H, 5·0. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%). No dimethyl ester was isolated. Esterification of the half-ester (I) with methanol and sulphuric acid yielded *methyl β-carbethoxy-β-fluorenylidenepropionate* (VI), compact yellow prisms (light petroleum) (70% yield), m. p. 93—94° (Found: C, 74·6; H, 5·7. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%).

Sodium methoxide (0·6 g.) was added to the ester (VIII) (1·7 g.) and benzaldehyde (1 c.c.) in sodium-dried ether (20 c.c.) and kept for 5 days. The brown precipitate was washed with ether and dissolved in water. Concentrated hydrochloric acid gave a very sticky solid which was extracted with ether. The ether was washed with water, dried (Na_2SO_4), and evaporated to a brown oil, which was dissolved in boiling benzene. From the cold solution α-benzylidene-α′-fluorenylidenesuccinic acid was deposited, orange crystals (chlorobenzene), m. p. 204—206° (lit., 206—208°).

Fluorenone (9 g.) condensed with ethyl succinate (17·5 g.) in the presence of sodium hydride (2·4 g.) to give β-carbethoxy-β-fluorenylidenepropionic acid (6·7 g., 42%), the corresponding dibasic acid (1·4 g., 10%), difluorenylidenesuccinic acid (0·35 g., 3·2%), and 0·4 g. of a compound, m. p. 125—127° after crystallisation from benzene–light petroleum, which is probably ethyl 1 : 4-diketo*cyclo*hexane-2 : 5-dicarboxylate.

Fluorenylidenesuccinic anhydride (IX) was prepared by two methods. (*a*) The half-ester (I) (0·7 g.) was heated under reflux in acetic anhydride (5 ml.), glacial acetic acid (5 ml.), and zinc chloride (0·01 g.) for 4 hours. On cooling, the anhydride (0·45 g.) separated in needles, which on crystallisation from glacial acetic acid had m. p. 203—205°. It gave no m. p. depression with the dicarboxylic acid, probably owing to anhydridisation of the latter. (*b*) The di-acid (II) (1 g.) was kept in acetyl chloride (40 ml.) for 1 hour. Benzene was then added to dissolve the precipitate, and the solution warmed gently to remove the acetyl chloride. On cooling, the anhydride separated in yellow elongated prisms, m. p. 211—212°, giving no m. p. depression with the above anhydride or the di-acid (Found: C, 77·0; H, 3·8. $C_{17}H_{10}O_3$ requires C, 77·8; H, 3·8%).

Fluorenylidenesuccinic acid (II) (0·4 g.) was heated under reflux in glacial acetic acid (10 ml.), and zinc dust (2 g.) added. After 20 minutes the colourless solution was poured into water (90 ml.) and extracted with ether. The ethereal layer was twice extracted with aqueous potassium carbonate (5%), which on acidification yielded *9-fluorenylsuccinic acid* (V), 0·37 g., m. p. 181—184°, identical with a sample obtained from fluorene and maleic anhydride as needles (benzene–light petroleum), m. p. 185—186° (cf. Alder, Vagt, and Pascher, *Ber.*, 1942, **75**, 1501) (Found: C, 72·0; H, 5·6. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%). The dimethyl esters were also identical.

Reduction of β-Carbethoxy-β-fluorenylidenepropionic Acid (I).—The half-ester (1 g.) was dissolved in glacial acetic acid (20 ml.), zinc dust (3 g.) added, the mixture heated under reflux for 1 hour and poured into water (60 ml.), and the white precipitate extracted with ether. The ether was extracted with aqueous potassium carbonate, which on acidification gave *β-carbethoxy-β-9-fluorenylpropionic acid* (IV) (0·91 g.), needles (benzene), m. p. 168—169° (Found: C, 73·5; H, 6·0. $C_{19}H_{18}O_4$ requires C, 73·5; H, 5·85%). It was hydrolysed by boiling with 10% sodium hydroxide for 30 minutes; acidification gave 9-fluorenylsuccinic acid, m. p. 182—185°, which was esterified with methanol and concentrated sulphuric acid to *methyl β-carbethoxy-β-9-fluorenylpropionate* (VII), m. p. 93—94°, needles (methanol), identical with the product obtained by reducing methyl β-carbethoxy-β-fluorenylidenepropionate (VI) with zinc dust and glacial acetic acid (Found: C, 73·4; H, 6·25. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%).

β-Bromo-β-carbethoxy-β-9-hydroxy-9-fluorenylpropionic Acid Lactone (XI).—β-Carbethoxy-β-fluorenylidenepropionic acid (1 g.) in glacial acetic acid (3 ml.) was treated with bromine (0·6 g.). The solution when kept deposited crystals of the *bromo-lactone* (XI), which were crystallised from benzene–light petroleum (b. p. 60—80°); needles, m. p. 149—150°; yield 0·65 g. (Found: Br, 20·5. $C_{19}H_{15}O_4Br$ requires Br, 20·6%). A further 0·25 g. was obtained from the original solution by addition of water and

subsequent purification. It was also prepared similarly by the bromination of the di-ester (VIII). The bromo-lactone (0·5 g.) was dissolved in dry pyridine (5 c.c.) and the solution kept just below the b. p. for 1 hour. Addition of water (25 c.c.) gave the *lactone* of β-carbethoxy-β-9-hydroxy-9-fluorenylacrylic acid (XIII), needles (0·28 g.) (methanol), m. p. 124—125° (Found: C, 74·55; H, 4·6. $C_{19}H_{14}O_4$ requires C, 74·5; H, 4·6%). This gave with hot 10% sodium hydroxide for 30 minutes, followed by acidification, the *carboxy-lactone* (XII), also obtained as follows. The bromo-lactone (0·5 g.) was heated under reflux for 40 minutes with glacial acetic acid (5 c.c.) and hydrobromic acid (34%; 5 c.c.), and the mixture poured into water (40 c.c.). The precipitate was extracted with ether, and from the ethereal layer by shaking with aqueous potassium carbonate, followed by acidification, the carboxy-lactone (XII) was obtained in prisms (chlorobenzene), m. p. 230—231° (Found: C, 73·4; H, 3·75. $C_{17}H_{10}O_4$ requires C, 73·4; H, 3·6%). It was also obtained from the carbethoxy-lactone (XIII) by boiling with 10% sodium hydroxide for 30 minutes. The butenolide (XII) (0·1 g.) was heated under reflux in glacial acetic acid (5 c.c.) with zinc dust (1 g.), the solution decanted into water, and the oil extracted with ether. Extraction of the ethereal layer with aqueous potassium carbonate, followed by acidification with concentrated hydrochloric acid, gave a white precipitate (0·07 g.) of 9-fluorenylsuccinic acid (V), m. p. 185—186°.

β-Bromo-β-carbethoxy-β-9-hydroxy-9-fluorenylpropionic acid lactone (XI) (0·5 g.) was heated under reflux in glacial acetic acid (10 c.c.) with zinc dust (2 g.) for 1 hour, and the mixture added to water (50 c.c.). The precipitate on the usual treatment gave the acid (IV), m. p. 168—169° (no m. p. depression with a sample prepared as above), which was hydrolysed to 9-fluorenylsuccinic acid, m. p. 183—184°, by 10% sodium hydroxide, and esterified with methanol and sulphuric acid to methyl β-carbethoxy-β-9-fluorenylpropionate (VII).

β-Bromo-β-carboxy-β-9-hydroxy-9-fluorenylpropionic Acid Lactone (XIV).—Bromine (0·6 g.) was added to the acid (II) (1·0 g.), dissolved in hot glacial acetic acid (3 c.c.). After heating for 5 minutes, the solution was poured into water, and the oil extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4), and evaporated. The resulting oil was triturated with benzene, and the solid *lactone* (XIV) crystallised from chlorobenzene; m. p. 220—224°; yield 0·5 g. (Found: Br, 22·0. $C_{17}H_{11}O_4Br$ requires Br, 22·8%). A purer product was obtained by adding bromine (0·2 g.) in glacial acetic acid (2 c.c.) to a cold solution of the ethyl ester (III) (0·2 g.) in glacial acetic acid (2 c.c.) and keeping the solution for 3 hours. Water was added, the oily precipitate extracted with ether, and the ethereal layer washed several times with water, then with sodium hydrogen sulphite solution, and dried (Na_2SO_4). Evaporation gave an oil which on trituration with benzene yielded the bromo-lactone, purified by washing with benzene (3 c.c.); m. p. 224—225°, yield 0·075 g. Heating the bromo-lactone with 10% sodium hydroxide under reflux for 20 minutes and acidifying the clear solution with concentrated hydrochloric acid gave needles of the butenolide (XII), m. p. 228—230°.

Decarbethoxylation of β-Carbethoxy-β-9-fluorenylidenepropionic Acid (I).—The half-ester (I) (1 g.) was heated under reflux in a mixture of glacial acetic acid (20 c.c.) and hydrobromic acid (34%, 20 c.c.) for 4 hours. The solution was slowly cooled; the precipitate on crystallisation from benzene or ethanol deposited colourless needles (0·8 g.), m. p. 197—199°, undepressed when mixed with the lactone (XV) prepared as described below, and having a blue fluorescence. A similar result was obtained with the dibasic acid (II). The lactone was heated under reflux with red phosphorus (0·4 g.) and hydriodic acid (*d* 1·9, 5 c.c.) for 45 minutes, and the mixture added to water. The product was extracted with ether, and the ether shaken with sodium carbonate, which on acidification gave an oily solid which was extracted five times with 30-c.c. portions of boiling light petroleum (b. p. 100—120°). Cooling gave 0·47 g. of β-9-fluorenylpropionic acid (XVIII), m. p. 141—142°.

β-9-Fluorenylidenepropionic acid (XVI) (2·4 g.), prepared from acrylonitrile and fluorenol (Campbell and Fairfull, unpublished results), was dissolved in cold glacial acetic acid, and bromine (1·6 g.) added. After 3 hours, water was added and the precipitate was extracted several times with boiling light petroleum (b. p. 100—120°). On cooling 9: *β-dibromo-β-9-fluorenylpropionic acid* (XVII) (1·5 g.) separated; it crystallised from benzene (twice) in elongated prisms, m. p. 165—167° (Found: Br, 40·7. $C_{16}H_{12}O_2Br_2$ requires Br, 40·3%). The dibromo-acid (1·5 g.) was boiled in glacial acetic acid (10 c.c.) with zinc dust (5 g.) for 15 minutes, and the solution filtered. Addition of water and crystallisation of the precipitate from benzene gave needles, m. p. 197—199°, with a bright blue fluorescence, identical with the *lactone* (XV), prepared as follows. The acid (XVI) (8 g.) was heated under reflux with 10% sulphuric acid (150 c.c.) for 2 hours and poured into ice-water (150 g.). The crude lactone (7·7 g.) separated and crystallised from benzene in needles, m. p. 200—201° (Found: C, 81·2; H, 5·0. $C_{16}H_{12}O_2$ requires C, 81·3; H, 5·1%), with a bright blue fluorescence.

The acid (XVI) (2·4 g.) was catalytically reduced with Adams' platinum oxide catalyst in glacial acetic acid. The volume was then reduced to 10 c.c., and water added. The precipitate was extracted several times with boiling light petroleum (b. p. 100—120°), which on cooling deposited β-9-fluorenylpropionic acid (XVIII), m. p. 141—142° (50% yield) after several crystallisations from benzene (no m. p. depression when mixed with a sample prepared as above) (Found: C, 80·3; H, 6·25. Calc. for $C_{16}H_{14}O_2$: C, 80·6; H, 5·9%).

Di-9-fluorenylidenesuccinic Acid (XIX).—Fluorenone (9 g.) in ethyl succinate (13 g.) and sodium-dried ether (600 c.c.) was gradually stirred into a suspension of sodium methoxide (7·5 g.) in dry ether (200 c.c.) cooled in ice–salt. Stirring was continued for a further 3 hours, and the mixture kept in a refrigerator for 5 days and finally at room temperature for 1 day. The ether (containing 2·2 g. of fluorenone) was removed, water (1500 c.c.) added to the aqueous residue, and the mixture boiled. Concentrated hydrochloric acid gave a dark mass (9·5 g.) of the *acid* (XIX) which solidified on cooling and crystallised from methanol in yellow needles (3·5 g.), m. p. 212—213° (decomp.) (Found: C, 81·1; H, 4·3; *M*, 420—456. $C_{30}H_{18}O_4$ requires C, 81·45; H, 4·1%; *M*, 442). It was not esterified by methanol–sulphuric acid, but with diazomethane gave the *dimethyl* ester, yellow octahedra (toluene), m. p. 224—225° (Found: C, 80·9; H, 4·95. $C_{32}H_{22}O_4$ requires C, 81·7; H, 4·7%), which on hydrolysis with sodium hydroxide for 1 hour gave the original acid. Attempts to form the anhydride by boiling the acid with acetyl chloride, etc. were unsuccessful.

The acid (XIX) (0·5 g.) was heated in quinoline (20 c.c.) with copper bronze (0·05 g.) (temperature of oil-bath 180°) until evolution of carbon dioxide ceased. The solution was poured into dilute hydrochloric acid (100 c.c.), and the precipitate filtered off, washed with acetone, and crystallised from xylene. Orange-red needles of di-9-fluorenylidene-ethane separated; m. p. (uncorr.) 368—370°, sublimes just below the m. p. (lit., m. p. 372—374°) (Found: C, 94·5; H, 5·2. Calc. for $C_{28}H_{18}$: C, 94·8; H, 5·2%). This gives in nitrobenzene with aluminium chloride a red colour turning to dark green, and with cold fuming sulphuric acid a beautiful blue colour changing to green. The hydrocarbon (0·2 g.) in glacial acetic acid (30 c.c.) was heated under reflux for 1 hour with zinc dust (5 g.) until the red colour had disappeared. Di-9-fluorenylethylene (0·12 g.) separated; m. p. (uncorr.) 262—263°, after crystallisation from glacial acetic acid (lit., m. p. 267—268°). This hydrocarbon (0·1 g.) was heated under reflux with sodium amalgam in aqueous alcohol (30 c.c.) for 2 hours. The solution was decanted and filtered, and on cooling deposited di-9-fluorenylethane, which after crystallisation from benzene–light petroleum had m. p. 224—225° (lit., m. p. 224—225°).

The di-acid (XIX) (5 g.) was heated under reflux in acetic acid (600 c.c.) and 34% hydrobromic acid (400 c.c.) for 24 hours. The solution was poured into ice-water (2 l.), the precipitate dissolved in boiling ethanol (charcoal), the solution filtered, and water added until the solution became turbid. The *dilactone* (XX) separated as colourless prisms, m. p. 284—286° (Found: C, 81·5; H, 4·3. $C_{28}H_{18}O_4$ requires C, 81·45; H, 4·1%). It yielded, when heated under reflux with sodium hydroxide for 2 hours, a solution which on acidification gave the di-acid.

Thanks are due to the Anglo-Iranian Oil Co., Ltd., for a research grant, and to Mr. W. K. Buchanan for preparing a sample of α-(9-fluorenylidene)-β-benzylidenesuccinic acid.

THE UNIVERSITY OF EDINBURGH. [*Received, September 22nd,* 1948.

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235. *Absorption Spectra of Isomeric Aromatic Diazocyanides.*

By R. J. W. LE FÈVRE and I. R. WILSON.

Five pairs of isomeric diazocyanides have been examined in ethereal solution between 220 and 600 mμ. Differences between related forms are not great and lie more in $\varepsilon_{max.}$ than in $\lambda_{max.}$. The data are compatible with the geometrical explanation proposed originally by Hantzsch for these compounds.

IN this paper we describe the ultra-violet spectra of five pairs of isomeric diazocyanides, ethyl ether being the solvent throughout. Although the stable and unstable varieties of two of these structures have been previously examined spectroscopically (Dobbie and Tinkler, *J.*, 1905, **87**, 275; Hantzsch and Lifschitz, *Ber.*, 1912, **42**, 3011), we thought a reinvestigation with modern equipment desirable in view of the opinions expressed during a recent discussion (Hodgson, *Chem. and Ind.*, 1948, 270) on the formulation of a number of $-N{=}N-$ containing molecules.

Hodgson says: "When Dobbie and Tinkler and later Hantzsch and Lifschitz recorded the visual spectra of the alleged *cis*- and *trans*-diazocyanides, the *cis*- were found to be identical with the *trans*-graphs. Now Hantzsch never failed to use colour arguments when it suited his purpose, and I was amazed to find that after obtaining the same visual spectra for compounds which are yellow and red, and also having recorded the ready convertibility of *cis*- to *trans*-forms even at −5°, Hantzsch should not immediately have concluded that he had measured one and the same substance on both occasions to account for the identity." A little farther on he adds "I first pointed out that the identity of the Hantzsch spectra indicated identity of compound measured; for even if *cis*- and *trans*-forms really exist they should afford different visual spectra."

Dobbie and Tinkler, and Hantzsch and Lifschitz, of course, published their observations in the older, and rather rough, form of graphs showing oscillation frequency against layer thickness; yet, even so, we submit that these provide no justification for Hodgson's statements. The English authors reported on the isomeric forms of *p*-methoxy- and *p*-chloro-benzenediazocyanides, and the German on the corresponding 2:4:6-tribromo-derivatives. In all cases the spectra were shown as *similar but not identical.* Differences of $\lambda_{max.}$ are somewhat obscured by the method of presentation, but *differences of intensity are clearly indicated.* Such a situation is to be anticipated for geometrical isomers (Le Fèvre, Northcott, and Wilson, *Chem. and Ind.*, 1948, 732; cf. also Braude, *Ann. Reports*, 1945, **42**, 125).

Present work.—The solutes were prepared by methods already described (Anderson, Le Fèvre, and Savage, *J.*, 1947, 445; Anderson, Bedwell, and Le Fèvre, *ibid.*, p. 457). Ether was selected as the solvent since it had been used by Hantzsch and we desired particularly to check his findings. Solutions were made up immediately before examination. The spectra were recorded over the appropriate range 220—600 mμ with a Beckman photoelectric spectrophotometer, model DU. They are shown diagram-

FIG. 1.

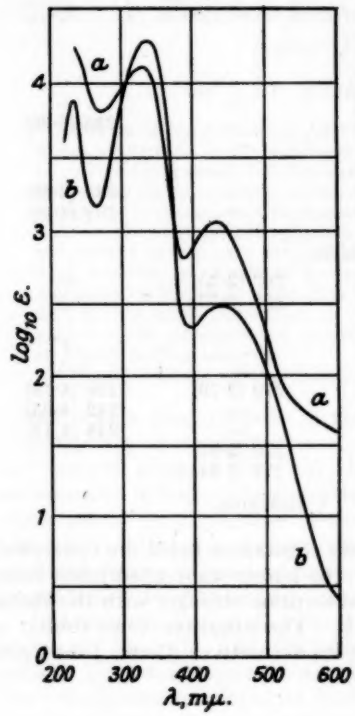


FIG. 2.

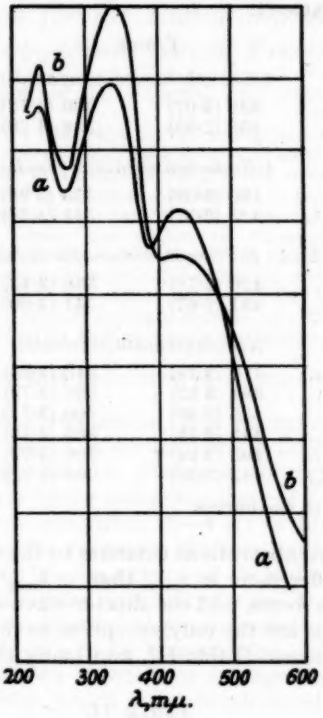


FIG. 3.

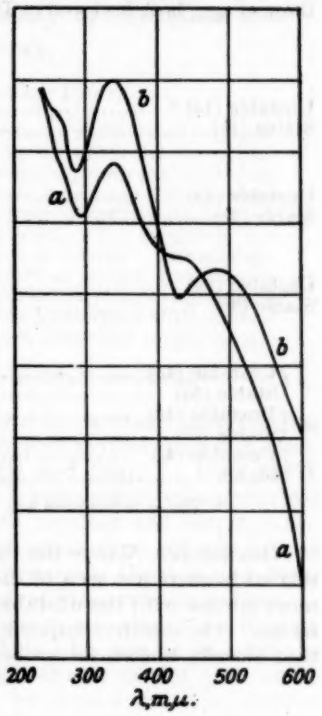


FIG. 4.

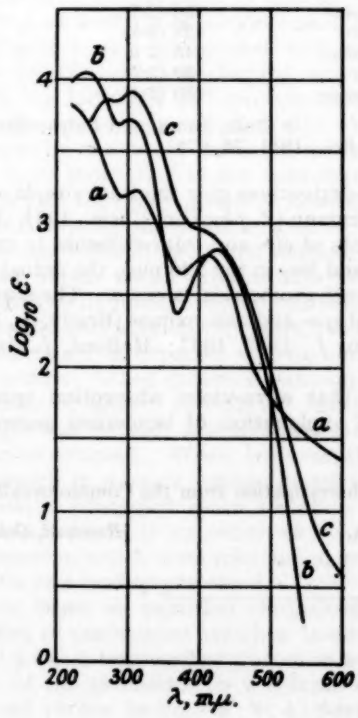
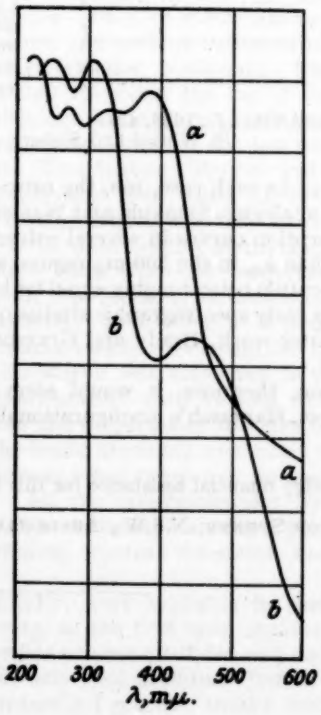


FIG. 5.



matically in Figs. 1—5 and summarised in Table I, values of $\lambda_{max.}$ being followed in parentheses by those of $\varepsilon_{max.}$ both here and in Table II.

TABLE I.

4-Chlorobenzenediazocyanides.				
Unstable (1*a*) *	432 (3·07)	330 (4·12)	—	—
Stable (1*b*)	438 (2·48)	338 (4·29)	—	235 (3·90)
4-Bromobenzenediazocyanides.				
Unstable (2*a*)	430 (3·08)	335 (3·96)	—	235 (3·80)
Stable (2*b*)	425 (2·77)	341 (4·50)	—	238 (4·09)
2 : 4 : 6-*Tribromobenzenediazocyanides.*				
Unstable (3*a*)	426 (2·76) †	338 (3·42)	262 (3·35) †	—
Stable (3*b*)	481 (2·67)	341 (4·00)	257 (3·77) †	—
Nitrobenzenediazocyanides.				
o-Unstable (4*a*)	410 (2·75)	310 (3·23)	—	—
o-Stable (5*a*)	388 (3·92)	330 (3·79)	270 (3·79)	220 (4·15)
m-Unstable (4*b*)	425 (2·82)	300 (3·71)	—	242 (4·05)
m-Stable (5*b*)	443 (2·19)	305 (4·13)	—	248 (4·14)
p-Unstable (4*c*)	405 (2·94) †	306 (3·92)	270 (3·87)	—
p-Stable	443 (2·38)	308 (4·22)	277 (3·94) †	

* These references are to the curves. † Inflexion.

Discussion.—Where the two absorptions common to the six substances listed are concerned, related isomers are seen to differ more in $\varepsilon_{max.}$ than in $\lambda_{max.}$, the longer-wave absorption being more intense with the unstable forms, and the shorter-wave absorption stronger with the stable forms. The *o*-nitro-compounds are the only exception to this. The situation seems similar to that already known for azobenzene (Table II), and many of its derivatives (Cook, Jones, and

TABLE II.

Solvent.	Configuration.	Absorptions and intensities.	
C_6H_6 *	*cis*-	430 (3·1)	*ca.* 300 (3·6)
	trans-	450 (2·7)	330 (4·3)
$CHCl_3$ †	*cis*-	438 (3·1)	324 (4·2)
	trans-	445 (2·5)	319 (4·3)
EtOH ‡	*cis*-	430 (3·1)	305 (3·4)
	trans-	450 (2·4)	320 (4·2)

* Le Fèvre and Vine, *J.*, 1938, 431. † Cook, Jones, and Polya, *ibid.*, 1939, 1315.
‡ Winkel and Siebert, *Ber.*, 1941, **74**, 670.

Polya, *loc. cit.*). In each case, too, the nitro-derivatives give the least simple spectra.

As to other analogies, Smakula and Wassermann (*Z. physikal. Chem.*, 1931, *A*, **155**, 353) have found the absorption curves in several solvents of *cis*- and *trans*-stilbenes to cross one another (ε_{trans} greater than ε_{cis} in the 300 mμ region, and less in the 220 mμ), the actual wave-lengths of maximum absorption being roughly equal for both geometrical isomers. The same characteristics are to be seen in early spectrographic studies of *syn*- and *anti*-oximes (Brady, *J.*, 1914, **105**, 2104), confirmed by later work (Brady and Grayson, *J.*, 1933, 1037; Raffouf, *J. Amer. Chem. Soc.*, 1946, **68**, 1765).

In conclusion, therefore, it would seem that ultra-violet absorption spectra display no evidence against Hantzsch's configurational explanation of isomerism among the aromatic diazocyanides.

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236. *A Modified Method for the End-group Assay of Amylose and Other Long-chain Starch Fractions.*

By E. J. Bourne, K. H. Fantes, and Stanley Peat.

The partition method of Bell (*J.*, 1944, 473) for the end-group assay of methylated starches is not applicable to the determination of the chain-length of amylose, in which the proportion of end-group is small, for the reason that a non-crystalline impurity accompanies the crystalline end-group (tetramethyl glucose) and is not separated from it in the silica column. This syrupy impurity is probably a pentamethyl disaccharide, and is formed from trimethyl glucose but not from tetramethyl glucose under the action of aqueous acid. To minimise the proportion of impurity formed, the method of Bell has been modified as follows. The methylated amylose is submitted to methanolysis and the resulting mixture of methyl glucosides is fractionally distilled. The first fractions, which contain all the tetramethyl methylglucoside and only a small proportion of trimethyl methylglucoside, are then hydrolysed with mineral acid and the products are separated by Bell's procedure. Minimum formation of the syrupy impurity is thus assured.

Starch and its components are best methylated in suspension in liquid ammonia.

There was a dual purpose in this investigation, first to measure the average chain-lengths of the fractions derived from potato starch by selective precipitation with thymol (Haworth, Peat, and Sagrott, *Nature*, 1946, **157**, 19; Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687), and secondly to find a reliable method for the end-group assay of 1 : 4-α-glucosidic polysaccharides which would be applicable to small quantities (2—4 g.) of both amylose and amylopectin. The latter object was to facilitate the complete examination of starch-type polysaccharides produced from glucose-1 phosphate by the agency of P- and Q-enzymes (Bourne and Peat, *J.*, 1945, 877) by eliminating the laborious synthesis of some 30 g. of these polysaccharides.

The thymol-precipitated amylose fraction of potato starch, which was shown by Bourne, Donnison, Haworth, and Peat (*loc. cit.*) to be blue-staining and to give rise to 96—99% of maltose by β-amylolysis, is now shown to have an average chain-length of 190 ± 10 units. The red-staining amylopectin fraction, which is not precipitated by thymol and gives maltose (*ca.* 50%) and a limit dextrin under the action of β-amylase (Bourne, Donnison, Haworth, and Peat, *loc. cit.*), is shown to have an average chain-length of 18 ± 1 units. These assays, which were made by a modification of the method published by Bell (*J.*, 1944, 473), were performed on 2·5 g. of methylated amylopectin and 2·5—4·2 g. of methylated amylose.

The polysaccharides were methylated with sodium and methyl iodide in liquid ammonia suspension at −70° (Freudenberg, Boppel, and Meyer-Delius, *Naturwiss.*, 1938, **26**, 123), a method which is less laborious and quicker than that involving the use of methyl sulphate in the presence of aqueous sodium hydroxide. Although some physical disaggregation occurs during methylation by the liquid ammonia method, as is shown by the low viscosities of the products, there is no shortening of the unit-chains (Freudenberg, Boppel, and Meyer-Delius, *loc. cit.*). Contrary to the observations of Hess and Krajnc (*Ber.*, 1940, **73**, 976), according to whom whole starch is more easily methylated by methyl sulphate–sodium hydroxide than are either amylose or amylopectin, we found amylose to be most readily methylated, amylopectin least readily, and starch at an intermediate rate. Thus after one methylation, involving six alternate additions of methyl iodide and sodium, the methoxyl contents of the products from amylose, starch, and amylopectin were, respectively, 43·5—44·8, 37·6, and 34·9%. This order of reactivity would be expected if steric hindrance effects were operative in the branched amylopectin structure. When defatted waxy-maize starch was subjected to the same treatment, either before or after "activation" by precipitation with alcohol from an aqueous paste, a sticky gel was formed, and this prevented the dispersal of the starch so effectively that no methylation occurred. When, however, the liquid ammonia was added to a suspension of waxy-maize starch in a small volume of anhydrous ether there was no swelling tendency and the methylation proceeded quite smoothly. All the polysaccharides were methylated until their methoxyl contents exceeded 43·2%. The trimethyl amylose preparations were tough filmy substances, which were resistant to grinding, whereas the starch- and amylopectin-ethers were brittle and readily powdered.

Two methods, based on partition chromatography, were available for end-group assays of small quantities of methylated starches, involving, in the first case, separation of 2 : 3 : 6-trimethyl and 2 : 3 : 4 : 6-tetramethyl glucose on a silica column (Bell, *loc. cit.*) and, in the second case, separation of the glucosides on a column of activated alumina (Jones, *J.*, 1944, 333). Bell's method was chosen because 2 : 3 : 4 : 6-tetramethyl glucose, unlike mixtures of its α-

and β-methylglucosides, is crystalline and therefore more easily recognised in its pure form. Bell's assay is a four-stage process: Stage I, hydrolysis of the methylated polysaccharide at 100° with a mixture of glacial acetic acid (5 parts) and 5% aqueous hydrochloric acid (10 parts); Stage II, removal of the acids; Stage III, extraction of an aqueous solution of the mixed sugars with nine equal volumes of chloroform and evaporation of the chloroform extracts to a syrup which contains all the tetramethyl glucose (" tetra ") and only 10% of the trimethyl glucose (" tri "); Stage IV, chromatography of a chloroform solution of the syrup on a silica–water column, under conditions such that the residue of " tri " is retained by the column, while the " tetra " passes through.

The efficiency of the partition (Stages III and IV) was ascertained by analysing artificial mixtures of tri- and tetra-methyl glucose, the molecular proportions of which ranged from 18 to 131 molecules of " tri " per molecule of " tetra." The recovered " tetra " fractions were all crystalline and had an average methoxyl content of 52·5%, which agreed well with the theoretical value, 52·6% (Table I). With one exception, the recovery of " tetra " was 88·2—95·4% and averaged 90·3%, compared with 93% quoted by Bell (*loc. cit.*) for Stage IV alone. An allowance for this consistently low recovery of tetramethyl glucose was made in all end-group assays, the factor employed being 90 ± 5%.

TABLE I.

Partition of Artificial Mixtures of " Tri " and " Tetra " by Bell's Method (Stages III and IV).

Wt. of mixed sugars (g.).	Mol. propn., " tri " : " tetra."	Recovery of " tetra " (%).	OMe of " tetra " (theory, 52·6) (%).
0·708	18	79·6	52·5
1·543	32	94·4	52·3
1·072	58	93·2	52·5
2·100	69	89·7	—
2·065	111	95·4	52·6
4·027	120	88·2	52·4
2·032	131	91·5	—
	Mean values:	90·3	52·5

TABLE II.

End-group Assays by Bell's Method (Stages I—IV).

Polysaccharide.	B.V.	Methyl ether. Wt. (g.).	Methyl ether. OMe (%).	" Tetra " fraction, OMe (%).	Chain-length.
Potato thymol-amylopectin	0·211	2·501	43·6	51·4	18 ± 1
Potato thymol-amylose	1·070	6·240	43·5	40·1	—
Potato thymol-amylose	1·160	10·076	44·3	39·0	—

Bell's end-group assay, applied, without modification, to methylated potato thymol-amylopectin (B.V., 0·211; Table II), gave an average chain-length of 18 ± 1.

Attempts to assay two samples of trimethyl amylose (Table II) by the same method yielded syrups, having OMe, 40·1 and 39·0%, instead of the crystalline samples of tetramethyl glucose which had resulted from the partition of artificial mixtures. In the amylopectin assay, previously mentioned, the " tetra " fraction had a slightly low methoxyl content (51·4%), but the error was within the accuracy limits of the assay. It is to be noted that Bell (*loc. cit.*) did not assay an amylose sample, but his " tetra " fractions derived from methylated rice starch possessed a slightly low methoxyl content, the error being insufficient seriously to affect the accuracy of his calculated chain-lengths. Thus it became clear that although the partition (Stages III and IV) was capable of yielding pure tetramethyl glucose from artificial mixtures of tri- and tetra-methyl glucose, in proportions which would be expected to result from assays on amylopectin, starch, and amylose, the whole assay (Stages I—IV) gave reasonably pure tetramethyl glucose from starch and amylopectin and very impure " tetra " from amylose. It seemed probable that Stages I and II (*i.e.*, the hydrolysis of the methylated polysaccharides and the removal of the acids) were introducing a chloroform-soluble impurity, the presence of which was more in evidence when the chain-length was high, as in an amylose.

Accordingly, prepared mixtures of tri- and tetra-methyl glucose were subjected to a complete " assay " (Stages I—IV). One mixture, corresponding to that of a trimethyl amylopectin, gave a crystalline tetramethyl glucose fraction in 87% yield, with OMe, 50·3%, while another, which corresponded to a trimethyl amylose, gave a syrupy " tetra " fraction in 232% yield,

with OMe, 40·3% (Table III). Pure samples of tri- and tetra-methyl glucose were separately submitted to a similar assay (Stages I—IV), and the results clearly revealed that the chloroform-soluble syrupy impurity arose from the action of acid on the trimethyl glucose and not on the tetramethyl glucose (Table IV). The syrup reduced Fehling's solution, was hydrolysed by aqueous acid, and had OMe, 36·2%. It was probably a pentamethyl disaccharide (OMe, 37·6%) arising from demethylation and " reversion " of trimethyl glucose (see Freudenberg and Boppel, *Ber.*, 1940, **73**, 609; Frahm, *Annalen*, 1944, **555**, 187).

TABLE III.

Partition of Artificial Mixtures of " Tri " and " Tetra " after Acid Treatment (Stages I—IV).

Wt. of mixed sugars (g.).	Mol. propn., " tri " : " tetra."	Recovery of " tetra " (%).	OMe of " tetra " (%).
1·191	19	87·0	50·3
4·011	119	232·0	40·3

TABLE IV.

Partition of Methyl Glucoses after Acid Treatment (Stages I—IV).

		Apparent " tetra " recovered.		
Sugar used.	Wt. of sugar (mg.).	Wt. (mg.).	Nature.	OMe of apparent " tetra " (%).
Trimethyl glucose	6245	36·1	Syrup	36·2
Tetramethyl glucose	61·4	52·6	Crystalline	52·3

TABLE V.

End-group Assays by the Modified Method.

		Methyl ether.		" Tetra " fraction,	Chain-
Polysaccharide.	B.V.	Wt. (g.).	OMe (%).	OMe (%).	length.
Potato starch	0·400	2·207	45·2	51·9	26 ± 1
Potato thymol-amylose	0·915	2·596	44·8	51·8	101 ± 5
Potato thymol-amylose	1·210	4·215	43·9	—	191 ± 10
Potato thymol-amylose *	1·210	3·550	43·9	52·0	187 ± 10
Waxy-maize starch	0·104	2·500	43·6	52·1	26 ± 1

* Hydrolysed with 2N-toluene-*p*-sulphonic acid instead of hydrochloric acid.

The effect of the syrup on the assay was more marked in the case of amylose because of the much higher proportion of " tri " to " tetra," and it was therefore essential that, in such cases, the proportion of " tri " should be diminished before the hydrolysis stage was reached. To this end a modification of the method of Bell was devised, which entailed methanolysis of the trimethyl polyglucose and fractional distillation of the glucoside mixture, two small distillate fractions being collected. The first fraction, consisting of all the tetramethyl methylglucoside and a small proportion of the trimethyl methylglucoside, was hydrolysed with aqueous hydrochloric acid and the tetramethyl glucose determined by the partition method. As will be seen from Table V, this " tetra " fraction, which was crystalline in each of the examples cited, had OMe, 51·9—52·1%. It is obvious that this " tetra " specimen still contained a small amount of the syrupy impurity, produced by the action of acid on the residual trimethyl methylglucoside, but it was possible to measure the amount of this impurity by submitting a similar weight of the second distillate fraction (which consisted only of trimethyl methylglucoside) to the same acid and partition treatments, and thus to calculate, by difference, the weight of pure tetramethyl glucose in the first fraction.

The modified method of assay was first tested on methylated potato starch, and the average chain-length (26 ± 1) thus calculated was in good agreement with the accepted value. A thymol-precipitated " amylose " fraction of potato starch (B.V., 0·915), which had previously been shown by a classical end-group assay (requiring, incidentally, 28 g. of the methylated polysaccharide) to have an average chain-length of 96 ± 5, was found by the modified assay, for which only 2·6 g. of the trimethyl derivative were required, to have average chains of 101 ± 5 units. Another thymol-amylose fraction (B.V., 1·210) containing less amylopectin impurity (as shown by its higher blue value) had chains 190 ± 10 units long. There is reason to believe that even this amylose contained a little branched-chain impurity, because fractions

with B.V. as high as 1·40 can be isolated from potato starch by the aluminium hydroxide method (Bourne, Donnison, Peat, and Whelan, *J.*, 1949, 1).

The chain-length of waxy-maize starch, determined by means of the modified technique, was found to be 26 ± 1 units, a value which was intermediate between previously reported values: 20 units (periodate method) and 18 units (classical assay) by Brown, Halsall, Hirst, and Jones (*J.*, 1948, 27), and 26—30 units (classical assay) by Haworth, Hirst, and Woolgar (*J.*, 1935, 177). Thus it would appear that waxy-maize starch, in spite of its lower B.V., has a longer average chain-length than potato thymol-amylopectin. Perhaps this is related to the fact that waxy-maize starch is precipitated from solution by iodine under conditions which will not cause the precipitation of potato thymol-amylopectin.

Experimental.

Precautionary Measures.—The essential precautions with regard to the absence of grease, purity of solvents, etc., which were taken by Bell (*loc. cit.*), were observed throughout this work.

Fractionation of Potato Starch.—The amylose and amylopectin samples were obtained from potato starch by selective precipitation with thymol, according to the "Standard Procedure" described by Bourne, Donnison, Haworth, and Peat (*loc. cit.*).

Determination of the Blue Value (B.V.) of a Polysaccharide.—The blue value of a polysaccharide is a measure of the blue component of the colour produced when the polysaccharide is stained with iodine under standard conditions (Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924).

Preparation of the Silica.—The silica used in the columns was prepared by the method of Gordon, Martin, and Synge (*Biochem. J.*, 1943, **37**, 79). Each batch was tested, both qualitatively by the staining method of Bell (*loc. cit.*) and quantitatively on mixtures of 2 : 3 : 6-trimethyl and 2 : 3 : 4 : 6-tetramethyl glucose, before being employed for end-group assays.

End-group Assay of Methylated Polyglucoses by Bell's Method.—A number of methylated polysaccharides of the starch type was assayed by Bell's method (*loc. cit.*), which involved hydrolysis for 5—7 hours on a boiling water-bath with a mixture of glacial acetic acid (5 parts) and 5% (w/v) hydrochloric acid (10 parts), removal of the acids, and separation of the tetramethyl glucose from the trimethyl glucose by partition between chloroform and water, first by simple extraction and then by means of a silica column. Each calculation is based on the weight of the mixture of methyl glucoses isolated from the hydrolysate and not on the weight of the polysaccharide ether.

(a) *Potato thymol-amylopectin* (*B.V.*, 0·211). From 2·501 g. of methylated amylopectin (OMe, 43·6%), 2·401 g. (approx. recovery, 88%) of mixed sugars were obtained. The crystalline tetramethyl glucose (OMe, 51·4%) isolated by partition weighed 126·5 mg., which, after allowance for a 90 ± 5% recovery from the column, corresponded to an average chain-length of 18 ± 1 units.

(b) *Potato thymol-amylose* (*B.V.*, 1·070). 6·240 G. of trimethyl amylose (OMe, 43·5%) gave, in turn, 6·252 g. (approx. recovery, 92%) of mixed sugars and 83·9 mg. of a syrupy "tetra" fraction (OMe, 40·1%).

(c) *Potato thymol-amylose* (*B.V.*, 1·160). Partition of the mixed sugars (10·393 g.; approx. recovery, 95%) derived from 10·076 g. of trimethyl amylose (OMe, 44·3%) gave 211·5 mg. of a syrupy "tetra" fraction (OMe, 39·0%).

Partition of Artificial Mixtures of Tri- and Tetra-methyl Glucose after Acid Treatment.—Each mixture was treated in exactly the same way, including "hydrolysis" with mixed acids for 5 hours, as the above polysaccharide ethers.

(a) *Molecular ratio*, 19 "*tri*" : 1 "*tetra*." 1·191 G. of this mixture yielded 54·9 mg. (recovery, 87·0%) of crystalline tetramethyl glucose (OMe, 50·3%).

(b) *Molecular ratio*, 119 "*tri*" : 1 "*tetra*." 4·011 G. of this mixture gave a syrupy "tetra" fraction (82·1 mg.; OMe, 40·3%), with an apparent recovery of 232%.

Acid Treatment of 2 : 3 : 6-Trimethyl Glucose.—Trimethyl glucose (6·245 g.) was heated on a boiling water-bath for 6½ hours with 5% (w/v) hydrochloric acid. The solution was neutralised with silver carbonate and filtered. Colloidal silver was removed from the filtrate with hydrogen sulphide, and the silver sulphide separated by filtration through a charcoal pad, which was then washed with a little water. The combined filtrate and washings were analysed by the partition method of Bell (*loc. cit.*). The "tetra" fraction was a reducing syrup (36·1 mg.) (Found: OMe, 36·2. Calc. for a pentamethyl disaccharide: OMe, 37·6%).

Acid Treatment of 2 : 3 : 4 : 6-Tetramethyl Glucose.—Tetramethyl glucose (61·4 mg.) was heated on a boiling water-bath for 6 hours with 5% (w/v) hydrochloric acid (10 c.c.). The solution was neutralised with silver carbonate and filtered. Colloidal silver was removed from the filtrate with hydrogen sulphide, and the silver sulphide collected on a charcoal pad. The combined filtrate and washings, when analysed by the partition method of Bell (*loc. cit.*), yielded 52·6 mg. (recovery, 86%) of crystalline tetramethyl glucose (OMe, 52·3%).

Modified End-group Assay of Methylated Polyglucoses.—A suspension of the dry methylated polysaccharide (*A* mg.) in dry methyl alcohol containing 1·5—2% (w/v) dry hydrogen chloride was heated under reflux for 9 hours, before being neutralised with a slight excess of lead carbonate. The lead salts were removed by filtration and washed with dry methyl alcohol. The filtrate and washings were combined and evaporated under reduced pressure in the presence of a little barium carbonate to a syrup, which was dried at 100°/200 mm. for 30 minutes. A dry ethereal solution of the syrup was filtered (in small portions) through sintered glass into a tared Widmer flask containing known weights of barium carbonate and glass wool. The solution was evaporated to a syrup, which was dried at 100°/200 mm. to constant weight (*B* mg.). The glucoside mixture was distilled at 0·01 mm., two distillate fractions (400—650 mg.; weights *C* mg. and *D* mg., respectively) being collected in tared

receivers. As a check that all the tetramethyl glucose was present in the first fraction, the refractive indices of the last drops of the first and second fractions were measured and found to be identical, within experimental error, in every case. The two distillate fractions were separately hydrolysed with 50 parts (by weight) of 5% (w/v) aqueous hydrochloric acid for 7 hours at 100°. The hydrolysates were neutralised with silver carbonate and filtered. In some cases hydrogen sulphide was passed through the filtrate and washings to remove colloidal silver, but this was not essential as the colloidal silver did not pass through the silica column. The filtrates and washings were analysed for tetramethyl glucose by Bell's partition method. In every case the first distillate fraction yielded crystalline tetramethyl glucose (*E* mg.) contaminated with only a trace of oily material, while the second distillate fraction invariably yielded a small amount (*F* mg.) of syrup.

The chain-lengths were calculated in the following way:

Wt. of tetramethyl glucose, corrected for syrupy impurity and losses in the column = $\frac{100}{90}\left[E - \frac{F(C-E)}{D}\right]$ mg. = *X* mg.

$$\therefore \text{ G.-mols. of tetramethyl glucose} = \frac{X}{236}.$$

$$\text{No. of G.-mols. in glucoside mixture} = \frac{B}{236}.$$

$$\therefore \text{ Chain-length} = \frac{B}{X} = \frac{0{\cdot}9\,B}{E - \frac{F(C-E)}{D}}$$

This method was applied to several methylated polysaccharides with the results shown below.

Polysaccharide.	Potato starch.	Potato thymol-amylose.	Potato thymol-amylose.	Potato thymol-amylose.*	Waxy-maize starch.
Blue value	0·400	0·915	1·210	1·210	0·104
Wt. of methylated polysaccharide (*A* mg.)	2207	2596	4215	3550	2500
Wt. of glucoside mixture (*B* mg.)	2472	2776	4724	3873	2709
Wt. of first distillate fraction (*C* mg.)	999·1	444·7	575·0	506·8	631·4
Wt. of second distillate fraction (*D* mg.)	967·8	435·1	645·0	482·0	622·1
Wt. of " tetra " from first fraction (*E* mg.)	96·2	35·2	27·3	22·8	99·5
Wt. of " tetra " from second fraction (*F* mg.)	12·9	11·0	5·9	4·1	7·2
OMe of " tetra " from first fraction (%)	51·9	51·8	—	52·0	52·1
Chain-length	26 ± 1	101 ± 5	191 ± 10	187 ± 10	26 ± 1

* In this case 2N-toluene-*p*-sulphonic acid was used instead of aqueous hydrochloric acid for hydrolysis of the glucoside mixture, and the neutralisation stage was omitted.

The authors are indebted to Professor Sir Norman Haworth, F.R.S., for the interest he has shown in this work.

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237. *Some Trinuclear Cyanine Dyes. Part III. Trinuclear Dimethin*merocyanines *and Intermediate Compounds.*

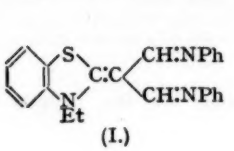
By FRANCES M. HAMER, RUSSELL J. RATHBONE, and BARBARA S. WINTON.

N-Alkyldihydro-derivatives of heterocyclic bases, with a dianilo*iso*propylidene group in the reactive position, were condensed with two mols. of compounds having a reactive cyclic methylene group, to give *trinuclear dimethin*mero*cyanines* with the chain :C<CH:CH:. The dianils were also condensed with one mol., to give intermediate *dinuclear dimethin*mero*cyanines* having an anilomethyl group. These intermediates yielded (1) *trinuclear dimethin*mero*cyanines* with two different nuclei terminating the chain, (2) *trinuclear dyes* having the chain :C<CH:CH:CH·, which were also obtained by an alternative method. Absorption maxima of methyl-alcoholic solutions of the new cyanines were compared with those of simpler ones having chain-systems which build up the complex branched chains.

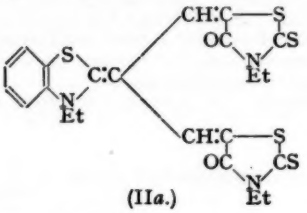
NEOCYANINES and intermediate dyes were prepared by condensing quaternary, heterocyclic ammonium salts, having a reactive methyl group, with dianilo-compounds, such as (I) (Hamer, Rathbone, and Winton, *J.*, 1947, 1434; 1948, 1872). Such a *neo*cyanine, in one of its resonating structures, has the three heterocyclic nuclei attached by the chain :C<CH:CH·CH:CH·.

A new type of dye characterised by having three nuclei and the chain :C<CH:CH:, has now been

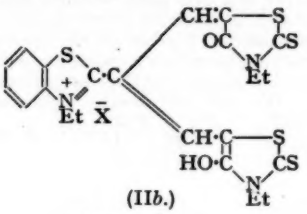
prepared by condensing a dianil containing the structure $:C<^{CH:NPh}_{CH:NPh}$ with a compound having a reactive cyclic methylene group. For instance, condensation of one molecule of (I) with two of 3-ethylrhodanine gave the *dye* (II*a*). Such a compound may be regarded as derived from the dimethin*mero*cyanine (III*a*). In theory, addition of acid to (II*a*) might give (II*b*), (II*c*), or



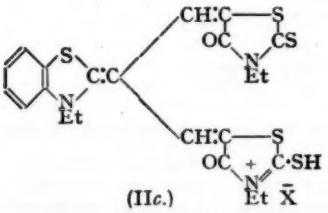
(I.)



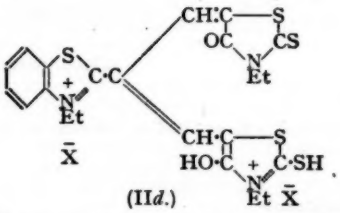
(II*a*.)



(II*b*.)



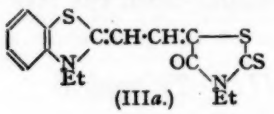
(II*c*.)



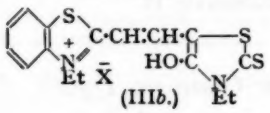
(II*d*.)

(II*d*), etc., which are derived from hypothetical acid forms, (III*b*), (III*c*), and (III*d*) of the dimethin*mero*cyanine. The formulæ (II*b*) and (II*d*) are also derivable from the trimethinoxonol (IV).* Other trinuclear *dyes* of this new type were made. Thus the 5-chloro-derivative of (I) was condensed with two molecules of 3-ethylrhodanine, also with two of 1-phenyl-3-ethyl-2-thiohydantoin to give (V), and with two of 2-diphenylamino-4-keto-Δ^2-thiazoline (Dixon and Taylor, *J.*, 1912, **101**, 558), to give (VI). Analogues of (I), in which the 3-ethylbenzthiazoline nucleus was replaced by 1-ethyl-1:4-dihydroquinoline, by 4-methyl-3-ethyl-Δ^4-thiazoline, and by 3-ethylbenzselenazoline, respectively, were condensed with 3-ethylrhodanine to give further *compounds* of this type; the last two analogues, as also (I) and its analogue having a 3-methylthiazolidine nucleus, were moreover each condensed with two molecules of 4-keto-2-thio-3-ethyltetrahydro-oxazole.

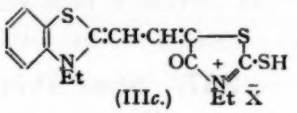
The absorption curves of methyl-alcoholic solutions of the eleven new dyes were plotted. Whereas neocyanines possessed narrow, well-defined curves (Hamer, Rathbone, and Winton,



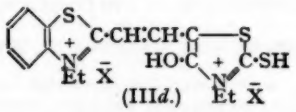
(III*a*.)



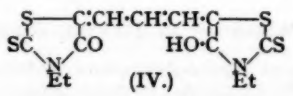
(III*b*.)



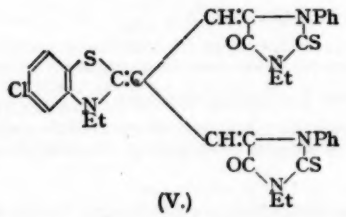
(III*c*.)



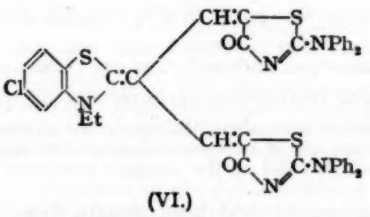
(III*d*.)



(IV.)



(V.)



(VI.)

loc. cit.), in the series with the chain $:C<^{CH:}_{CH:}$ a narrow absorption curve was exceptional, occurring only with dyes having a 4-methyl-Δ^4-thiazoline nucleus; most of the members had a broad curve, whilst (II*a*) itself had a curve with several maxima, such as might normally be attributed to impurities. The principal absorption maximum of each new trinuclear dye was compared

* For the meaning of the term "oxonol," see following paper.

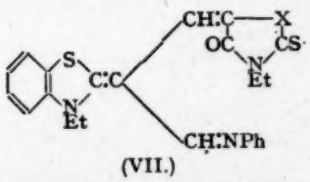
with that of the related dimethin*mero*cyanine, some of which were prepared for the purpose, but unfortunately only one of the corresponding oxonols was obtainable (Hamer and Winton, succeeding paper). The data are given in Table I. They are discussed together with those of the similar dyes contained in Table III.

TABLE I.

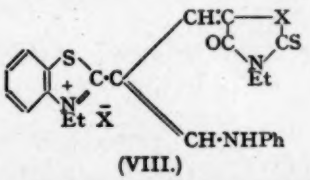
Dyes with chain: :C(CH:)(CH:)	Abs. max. (A.).	Dimethin-*mero*cyanines; chain: :CH·CH:	Abs. max. (A.).	Oxonol in alkali; chain: :CH·CH:CH	Abs. max. (A.).	Bathochromic shifts: Dimethin-*mero*cyanine to :C(CH:)(CH:)	Bathochromic shifts: :C(CH:)(CH:) to oxonol
4-q(Etrhod)(Etrhod)	5875	4-q(Etrhod)	6140 †	(Etrhod)(Etrhod)	6100 †	−265	225
bzth(Etrhod)(Etrhod) (IIa)	5600 etc.	bzth(Etrhod)	5300 †	(Etrhod)(Etrhod)	6100 †	300	500
bzth(tetraH-ox)(tetraH-ox)	5120	bzth(tetraH-ox)	5030 †	(tetraH-ox)(tetraH-ox)	—	90	—
Clbzth(Etrhod)	5080	Clbzth(Etrhod)	5220 †	(Etrhod)(Etrhod)	6100 †	−140	1020
Clbzth(thiohyd) (V)	5180	Clbzth(thiohyd)	5095 *	(thiohyd)(thiohyd)	—	85	—
Clbzth(Δ²-thiaz) (VI)	4955	Clbzth(Δ²-thiaz)	4925 *	(Δ²-thiaz)(Δ²-thiaz)	—	30	—
Me-th(Etrhod)	5720	Me-th(Etrhod)	5390 *	(Etrhod)(Etrhod)	6100 †	330	380
Me-th(tetraH-ox)	5350	Me-th(tetraH-ox)	5165 *	(tetraH-ox)(tetraH-ox)	—	185	—
bzSe(Etrhod)	5300	bzSe(Etrhod)	5260 *	(Etrhod)(Etrhod)	6100 †	40	800
bzSe(tetraH-ox)	5000	bzSe(tetraH-ox)	4990 *	(tetraH-ox)(tetraH-ox)	—	10	—
thiazoline(tetraH-ox)	4455 (5030)	thiazoline(tetraH-ox)	5075	(tetraH-ox)(tetraH-ox)	—	−620	—

* Private communication from Dr. L. G. S. Brooker and Mr. F. L. White.
† Hamer and Winton, succeeding paper.

By using comparatively mild conditions, the reaction could be stopped when the dianilo-intermediate had condensed with only one molecular equivalent of the compound having a



(VII.)



(VIII.)

reactive cyclic methylene group. For instance, (I) with 3-ethylrhodanine gave (VII; X = S) and with 4-keto-2-thio-3-ethyltetrahydro-oxazole gave (VII; X = O); (I) was also condensed

with one molecule of 3-carboxymethylrhodanine, and the 5-chloro-derivative of (I) with one molecule of 1-phenyl-3-ethyl-2-thiohydantoin or with one of 2-diphenylamino-4-keto-Δ^2-thiazoline. Analogues of (I) having a 4-methyl-3-ethyl-Δ^2-thiazoline or a 3-ethylbenzselenazoline nucleus were each condensed with one molecule of 3-ethylrhodanine, 4-keto-2-thio-3-ethyltetrahydro-oxazole, or 1-phenyl-3-ethyl-2-thiohydantoin; the analogue having a 3-ethylthiazolidine nucleus was similarly condensed with 3-ethylrhodanine, 4-keto-2-thio-3-ethyltetra-

TABLE

Anilomethyl Compounds. :C(CH:)(CH:NPh)	Abs. max. (A.). Alkali.	Acid.	Hypsochromic shifts, alkali to acid.	Dimethin *mero*cyanines; chain: :CH·CH:	Abs. max. (A.).	Anilo-ethylidene compounds. :CH·CH:NPh
bzth(Etrhod)anMe (VII; X = S)	5230	4400	830	bzth(Etrhod)	5300 *	bzth(anMe)
bzth(tetraH-ox)anMe (VII; X = O)	4975	4100	875	bzth(tetraH-ox)	5030 *	,,
bzth(rhod·CH_2·CO_2H)anMe	5055	4395	660	bzth(rhod·CH_2·CO_2H)	5025 *	,,
Clbzth(thiohyd)anMe	5110	4300	810	Clbzth(thiohyd)	5095 *	Clbzth(anMe)
Clbzth(Δ^2-thiaz)anMe	4835	4250	585	Clbzth(Δ^2-thiaz)	4925 *	,,
Me-th(Etrhod)anMe	4685	4465	220	Me-th(Etrhod)	5390 *	Me-th(anMe)
Me-th(tetraH-ox)anMe	4510	4150	360	Me-th(tetraH-ox)	5165 *	,,
Me-th(thiohyd)anMe	4860	4470	390	Me-th(thiohyd)	5290 *	,,
bzSe(Etrhod)anMe	5100	4400	700	bzSe(Etrhod)	5260 *	bzSe(anMe)
bzSe(tetraH-ox)anMe	4850	4105	745	bzSe(tetraH-ox)	4990 *	,,
bzSe(thiohyd)anMe	5055	4290	765	bzSe(thiohyd)	5140 *	,,
thiazoline(Etrhod)anMe	4825	4410	415	thiazoline(Etrhod)	4825	thiazoline(anMe)
thiazoline(tetraH-ox)anMe	4370	4110	260	thiazoline(tetraH-ox)	4575	,,
thiazoline(Δ^2-thiaz)anMe	4380	3990	390	thiazoline(Δ^2-thiaz)	4600	,,

* Private communication from Dr. L. G. S. Brooker and Mr. F. L. White.
† Hamer and Winton, succeeding paper.

hydro-oxazole, and 2-diphenylamino-4-keto-Δ^5-thiazoline. The conditions for success in the above condensations varied greatly according to the nature of the reactants. Although boiling pyridine was usually the medium, sometimes this was too drastic and a temperature of 50—70° was desirable. In other instances still milder conditions were necessary, comprising condensation in boiling, or even in ice-cold, absolute alcohol.

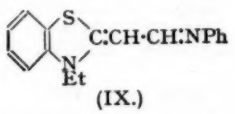
In Table II the absorption maxima of basified methyl-alcoholic solutions of intermediate

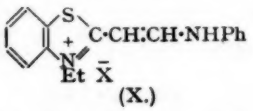
II.

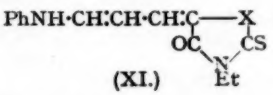
Abs. max. (A.). Base.	Salt.	Bathochromic shifts, base to salt.	Anilino-allylidene compounds; chain : :CH·CH:CH·NHPh	Abs. max. (A.).	Bathochromic shifts (A.). AniloMe base to dimethin-*mero*-cyanine.	Bases. Anilo-ethyl-idene to AniloMe.	Salts. Anilo-ethyl-idene to AniloMe.	AniloMe salt to anilino-allylidene compound.
3935‡	4175‡	240	Etrhod / anMe	4775 (alk.) †	70	1295	225	375
,,	,,	,,	tetraH-ox / anMe	4460 †	55	1040	−75	360
,,	,,	,,	rhod·CH_2·CO_2H / anMe	4800 (acid) †	−30	1120	220	405
4075‡	4205‡	130	thiohyd / anMe	4650 †	−15	1035	95	350
,,	,,	,,	Δ^2-thiaz / anMe	4680 (acid) †	90	760	45	430
4090‡	4030‡	−60	Etrhod / anMe	4775 (alk.) †	705	595	435	310
,,	,,	,,	tetraH-ox / anMe	4460 †	655	420	120	310
,,	,,	,,	thiohyd / anMe	4650 †	430	770	440	180
3940‡	4235‡	295	Etrhod / anMe	4775 (alk.) †	160	1160	165	375
,,	,,	,,	tetraH-ox / anMe	4460 †	140	910	−130	355
,,	,,	,,	thiohyd / anMe	4650 †	85	1115	55	360
3585‡	3660‡	75	Etrhod / anMe	4775 (alk.) †	0	1240	750	365
,,	,,	,,	tetraH-ox / anMe	4460 †	205	785	450	350
,,	,,	,,	Δ^2-thiaz / anMe	4680 (acid) †	220	795	330	690

‡ See Hamer, Rathbone, and Winton, *J.*, 1947, 954, for data about 3-ethyl-2-aniloethylidenebenzthiazoline, 5-chloro-3-ethyl-2-aniloethylidenebenzthiazoline, 4-methyl-3-ethyl-2-aniloethylidene-Δ^4-thiazoline, 3-ethyl-2-aniloethylidenebenzselenazoline, 3-ethyl-2-aniloethylidenethiazolidine, and corresponding salts.

dyes, characterised by the chain :C<CH:<CH:NPh, were compared on the one hand with those of methyl-alcoholic solutions of parent dimethin*mero*cyanines having the chain :CH·CH:, and on the other with alkaline methyl-alcoholic solutions containing parent bases with the chain :CH·CH:NPh. Thus (VII; X = S) was correlated with (III*a*) and with (IX). Further, the absorption maxima of acidified methyl-alcoholic solutions of intermediate dyes containing salts such as (VIII) were compared with acidified solutions containing quaternary salts, such as (X), and also with heterocyclic anilinoallylidene compounds such as (XI; X = S). Whereas on passing from five parent aniloethylidene bases to the corresponding salts there was only one hypsochromic shift, of 60 A., and four bathochromic, varying from 75 to 295 A., yet on passing


(IX.)


(X.)


(XI.)

from dinuclear anilomethyl bases (such as VII) to acid salts (such as VIII), all fourteen shifts were hypsochromic, varying from 220 to 875 A. With the somewhat similar anilomethyl compounds of Part II (*J.*, 1948, 1872), ten out of twelve showed a hypsochromic shift on passing from base to salt. On passing from each of the present new anilomethyl bases to the related dimethin*mero*cyanine, there were two hypsochromic shifts, of 15 A. and 30 A., one case of no change, and eleven bathochromic shifts, which varied from 55 to 705 A. On passing from mononuclear aniloethylidene bases (*e.g.*, IX) to the corresponding dinuclear anilomethyl bases (*e.g.*, VII), the shifts were all bathochromic, varying in the fourteen instances from 420 to 1295 A.; so also with the similar substances of Part II, all twelve shifts were bathochromic (*loc. cit.*). On passing from the mononuclear β-anilinovinyl salts (*e.g.*, X) to the corresponding acidified dinuclear intermediate compounds (*e.g.*, VIII), ten of the twelve shifts of absorption maximum were bathochromic, varying from 45 to 750 A., and the other two were hypsochromic, of 75 A. and 130 A. It seemed logical to compare the mononuclear heterocyclic compounds having the chain :CH·CH:CH·NHPh, *e.g.*, (XI), with the acidified dinuclear anilomethyl compounds, *e.g.*, (VIII), having the chain ·CH·C:CH·NHPh, and here, with fourteen pairs, the absorption maximum of the mononuclear compound always lay at a longer wave-length than that of its dinuclear derivative, the amounts varying from 180 to 690 A.

TABLE III.

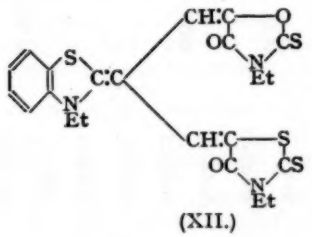
Dyes with chain: :C<CH:<CH:	Abs. max. (A.).	Dimethin*mero*cyanines: chain: :CH·CH:	Abs. max. (A.).	Bathochromic shifts (A.). Dimethin*mero*cyanine to :C<CH:<CH:
bzth<Etrhod<tetraH-ox (XII)	5475	bzth<Etrhod	5300	175
		bzth<tetraH-ox	5030	445
Me-th<Etrhod<tetraH-ox	5545	Me-th<Etrhod	5390 *	155
		Me-th<tetraH-ox	5165 *	380
bzSe<Etrhod<tetraH-ox	5190	bzSe<Etrhod	5260 *	−70
		bzSe<tetraH-ox	4990 *	200

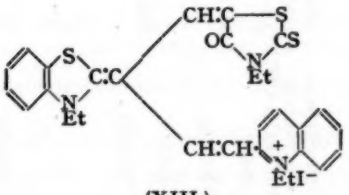
* Private communication from Dr. L. G. S. Brooker and Mr. F. L. White.

The new intermediate compounds with the chain :C<CH:<CH:NPh made it possible to arrive at dyes having the chain :C<CH:<CH: but differing from those in the earlier part of this paper in that the nuclei terminating the trimethin chain are dissimilar instead of similar. Theoretically each of these new dyes may be reached by either of two routes. We prepared three such dyes. The

first was obtained by condensing (VII; X = O) with 3-ethylrhodanine and is represented by (XII). In the other two the 3-ethylbenzthiazoline nucleus of (XII) was replaced by the 4-methyl-3-ethyl-Δ^4-thiazoline nucleus and the 3-ethylbenzselenazoline nucleus, respectively, but each was prepared by condensing the analogue of (VII; X = S) with 4-keto-2-thio-3-ethyltetrahydro-oxazole.

The absorption maxima of methyl-alcoholic solutions of these new dyes are correlated in Table III with those of the related dimethin*mero*cyanines. Whereas each dye having the chain $:C<^{CH:}_{CH:}$ in Table I was comparable with one dimethin*mero*cyanine, each in Table III was comparable with two such parent dyes. Summarising the two tables together, the shift of absorption maximum in passing from dimethin*mero*cyanine to trinuclear dye was bathochromic in thirteen out of seventeen instances, the values varying from 10 to 445 A., whilst the four hypsochromic values varied from 70 to 620 A. The absorption maximum of an alkaline solution of the oxonol (IV) was correlated with those of solutions of five trinuclear dyes having the chain $:C<^{CH:}_{CH:}$. It always lay at a longer wave-length, the values of the differences varying from 225 to 1020 A.


(XII.)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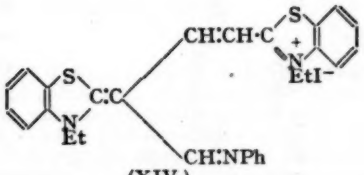
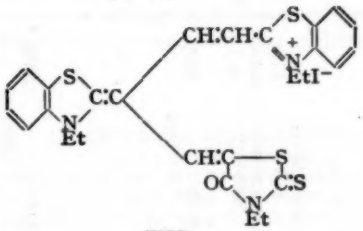
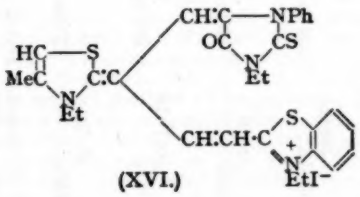

(XIV.)


(XV).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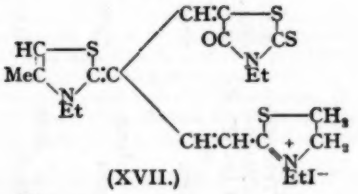
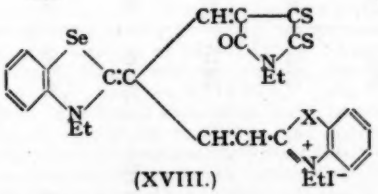

(XVII.)


(XVIII.)

By condensing the new type of intermediate dye with a quaternary salt having a reactive methyl group, yet another new kind of dye, characterised by possessing the chain $:C<^{CH:CH\cdot}_{CH:}$, was obtained. Thus (XIII) was prepared by condensation of (VII; X = S) with quinaldine, ethiodide. Dyes of this new group are also obtainable by a second route, according to which the intermediate dyes of Part II (*J.*, 1948, 1872) are condensed with compounds having a reactive cyclic methylene group. Thus condensation of (XIV) (*loc. cit.*) with 3-ethylrhodanine gave

TABLE IV.

Dye with chain : :C(CH:CH·)(CH:)	Abs. max. (A.).	Trimethincyanines : :CH·CH:CH·	Abs. max. (A.).	Dimethin-*mero*cyanines : :CH·CH:	Abs. max. (A.).	Tetramethin-*mero*cyanines : :CH·CH:CH·CH:	Abs. max. (A.).	Bathochromic shifts (A.). Chain : :CH·CH:CH· to CH:CH·(:C<CH:)	Chain : :CH·CH: to CH:CH·(:C<CH:)	Chain : :CH·CH:CH·CH: to CH:CH·(:C<CH:)
bzth(2q)Etrhod (XIII)	6080	bzth(2q)	5600 ¶	bzthEtrhod	5300	(2-q)Etrhod	6575 ‖	480	780	−495
bzth(bzth)Etrhod (XV)	5750	bzth(bzth)	5570 †	,,	,,	(bzth)Etrhod	5950 ‖	180	450	−200
Me-th(bzth)Etrhod	5750	Me-th(bzth)	5470 §	Me-thEtrhod	5390 *	,,	,,	280	360	−200
Me-th(bzbzth)Etrhod	5945	Me-th(bzbzth)	5660 ‖	,,	,,	(bzbzth)Etrhod	—	285	555	—
Me-th(thiazoline)Etrhod (XVII)	5360	Me-th(thiazoline)	4995 §	,,	,,	(thiazoline)Etrhod	5700 ‖	365	−30	−340
Me-th(bzth)thiohyd (XVI)	5765	Me-th(bzth)	5470 §	Me-ththiohyd	5290 *	(bzth)thiohyd	5650 ‖	295	475	115
bzSe(bzth)Etrhod (XVIII; X = S)	5800	bzSe(bzth)	5620 ‡	bzSeEtrhod	5260 *	(bzth)Etrhod	5950 ‖	180	540	−150
bzSe(bzbzth)Etrhod	5930	bzSe(bzbzth)	5810 ‡	,,	,,	(bzbzth)Etrhod	—	120	670	—
bzSe(bzSe)Etrhod (XVIII; X = Se)	5820	bzSe(bzSe)	5700 †	,,	,,	(bzSe)Etrhod	5590 ‖	120	560	230

* Private communication from Dr. L. G. S. Brooker and Mr. F. L. White.
† Fisher and Hamer, *Proc. Roy. Soc.*, 1936, *A*, **154**, 703.
‡ Beilenson, Fisher, and Hamer, *ibid.*, 1937, *A*, **163**, 138.
§ Hamer, Rathbone, and Winton, *J.*, 1948, 1872.
‖ Hamer and Winton, succeeding paper.
¶ 5780 A. is given by Brooker and Sprague (*J. Amer. Chem. Soc.*, 1941, **63**, 3203).

(XV). Two more *dyes* of this type were prepared by condensing an analogue of (VII; X = S), having a 4-methyl-3-ethyl-Δ^4-thiazoline in place of the benzthiazoline nucleus, with 2-methylbenzthiazole ethiodide and with its 6 : 7-benz-derivative, respectively; a third (XVI) was also obtained by this type of reaction. (XVII), however, was obtained by reaction of the appropriate intermediate of the other type (*loc. cit.*) with 3-ethylrhodanine. An analogue of (VII; X = S), having the 3-ethylbenzselenazoline in place of the 3-ethylbenzthiazoline nucleus, was condensed with 2-methylbenzthiazole ethiodide to give (XVIII; X = S), with 2-methyl-6 : 7-benzbenzthiazole ethiodide to give the 6 : 7 benz-derivative of (XVIII; X = S), and with 2-methylbenzselenazole ethiodide to give (XVIII; X = Se).

The absorption maximum of each new dye having the chain $:C<\begin{matrix}CH:\\CH:CH\cdot\end{matrix}$ may be compared with that of a trimethincyanine, of a dimethin*mero*cyanine, and of a tetramethin*mero*cyanine. It appears from Table IV that with all nine pairs there was a bathochromic shift on passing from trimethincyanine to trinuclear dye, these shifts varying from 120 to 480 A. With eight out of nine pairs, there was a bathochromic shift on passing from dimethin*mero*cyanine to trinuclear dye, the values of the shifts varying from 360 to 780 A., and there was one hypsochromic shift of 30 A. On passing from tetramethin*mero*cyanine to trinuclear dye, there were, however, out of seven pairs, only two bathochromic shifts, of 115 A. and 230 A., the other five being hypsochromic, varying from 150 to 495 A.

Photographic tests were carried out on gelatino-bromide plates except where otherwise stated. Some of the anilomethyl intermediate dyes sensitised strongly but the trinuclear dyes with the chain $:C<\begin{matrix}CH:\\CH:\end{matrix}$ sensitised only weakly and sometimes desensitised, whilst those with the chain $:C<\begin{matrix}CH:\\CH:CH\cdot\end{matrix}$ were mostly characterised by possessing only desensitising properties.

Nomenclature.—In the experimental section of the paper, the nomenclature is that explained in Part I (*J.*, 1947, 1434), the shorter methin chain being taken as the fundamental one, as is done there and in Part II (*J.*, 1948, 1872). All the new dyes of the present paper are therefore named as dimethin*mero*cyanines, the nomenclature of which is explained elsewhere (Hamer and Winton, succeeding paper).

Experimental.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzthiazoline*)][β-*methin*-5′-(3′-*ethylrhodanine*)]*dimethin*mero*cyanine* (II*a*).—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (I) (0·38 g.; 1 mol.), 3-ethylrhodanine (0·48 g.; 3 mols.), anhydrous sodium acetate (0·49 g.; 6 mols.), and acetic anhydride (5 c.c.) were heated together at 140—150° for 10 minutes. Absolute ether (20 c.c.) precipitated a solid from the reaction mixture. After washing with ether and with water (0·41 g. left), this was recrystallised from pyridine and obtained in 64% yield. It was dried in a vacuum at 60—80° and analysed by the method of Carius, which conditions were used throughout this work unless otherwise stated (Found : S, 31·1. $C_{22}H_{21}O_3N_3S_5$ requires S, 30·85%). The green and gold crystals had m. p. 229°, with previous shrinking. The broad absorption band had maxima at 5090, 5225, 5350, and 5600 A. The compound was a photographic desensitiser.

When the condensing agent was hot pyridine, the product was liable to consist of a mixture of (II*a*) with [5-(3-ethylrhodanine)][2-(3-ethylbenzthiazoline)]-β-anilomethyldimethin*mero*cyanine (VII; X = S).

In a second method of preparation, (VII; X = S) (0·45 g.; 1 mol.), 3-ethylrhodanine (2 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (10 c.c.) were stirred together at 140—150° for 5 minutes. The *dye* was precipitated with absolute ether, washed (0·45 g. obtained), and recrystallised from pyridine, resulting in 70% yield (Found : S, 30·8%).

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro-oxazole*)][2-(3-*ethylbenzthiazoline*)][β-*methin*-5′-(4′-*keto*-2′-*thio*-3′-*ethyltetrahydro-oxazole*)]*dimethin*mero*cyanine*.—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (1·03 g.; 1 mol.), 4-keto-2-thio-3-ethyltetrahydro-oxazole (2 mols.), anhydrous sodium acetate (8 mols.), and acetic anhydride (13 c.c.) were heated together at 140—150° for 2 minutes. After cooling, filtering off, and washing with water, the residue (0·55 g.) was recrystallised from pyridine (5 c.c.) and gave a 37% yield (Found : S, 19·75. $C_{22}H_{21}O_4N_3S_3$ requires S, 19·75%). The dark red crystals darkened from 210° and had m. p. 228° (decomp.). The broad absorption curve had its maximum at 5120 A. The *dye* sensitised weakly to 6200 A., with the maximum at 5600 A., and depressed the normal blue speed.

[5-(3-*Ethylrhodanine*)][2-(5-*chloro*-3-*ethylbenzthiazoline*)][β-*methin*-5′-(3′-*ethylrhodanine*)]*dimethin*mero*cyanine*.—5-Chloro-3-ethyl-2-dianilo*iso*propylidenebenzthiazoline (2·60 g.; 1 mol.), 3-ethylrhodanine (3 mols.), and pyridine (25 c.c.) were stirred together at 130—135° for 5 minutes. The liquid was treated with water and cooled and some dye was filtered off (0·68 g.). To obtain more, the filtrate was extracted with ether and the extract concentrated and treated with water (1·22 g. obtained). The total product (1·90 g.) was freed from a brown impurity by Soxhlet extraction with ether and the residue (1·04 g.), after recrystallisation from pyridine (10 c.c. per g.), gave a 23% yield (Found : Cl, 6·75. $C_{22}H_{20}O_2N_3ClS_5$ requires Cl, 6·4%). The bronze powder had m. p. 128—130° (decomp.), with previous shrinking. The broad absorption curve had its maximum at 5080 A. Weak sensitising was from 5500 to 5900 A., with strong decrease of blue sensitivity.

[5-(1-*Phenyl*-3-*ethyl*-2-*thiohydantoin*)][2-(5-*chloro*-3-*ethylbenzthiazoline*)][β-*methin*-5′-(1′-*phenyl*-3′-*ethyl*-2′-*thiohydantoin*)]*dimethin*mero*cyanine* (V).—The reaction mixture from 5-chloro-3-ethyl-2-dianilo-

*iso*propylidenebenzthiazoline (3·12 g.; 1 mol.), 1-phenyl-3-ethyl-2-thiohydantoin (3 mols.), anhydrous sodium acetate (6 mols.), and acetic anhydride (20 c.c.), after 10 minutes at 140—150°, was treated with ether (120 c.c.), and sodium acetate was filtered off. The ether was distilled off from the filtrate, and the residual liquid treated with water. The resultant sticky product was recrystallised from methyl alcohol (300 c.c.) (2·85 g. obtained). After boiling out with, and recrystallising from, methyl alcohol (8 c.c., 300 c.c.), the yield was 13% (Found: Cl, 5·45. $C_{34}H_{30}O_2N_5ClS_2$ requires Cl, 5·3%). The dark green crystals had m. p. 174° (decomp.). The broad absorption curve had its maximum at 5180 A. The *dye* decreased the normal photographic sensitivity, whilst conferring extra sensitivity up to 6700 A., with the maximum effect at 6150 A.

[5-(2-*Diphenylamino*-4-*keto*-Δ^2-*thiazoline*)][2-(5-*chloro*-3-*ethylbenzthiazoline*)][*β*-*methin*-5′-(2′-*diphenylamino*-4′-*keto*-$\Delta^{2'}$-*thiazoline*)]*dimethin*merocyanine (VI).—This was similarly prepared, 2-diphenylamino-4-keto-Δ^2-thiazoline being used instead of the thiohydantoin. Ether precipitated the *product*; after water-washing the yield was 78% and after recrystallisation from pyridine (3 c.c. per g.) 44% (Found: Cl, 4·7. $C_{43}H_{30}O_2N_5ClS_2$ requires Cl, 4·6%). The terra-cotta powder had m. p. 193—194° (decomp.). The broad absorption curve had its maximum at 4955 A., sloping down to a shoulder at 4700 A. There was no photographic sensitisation but slight depression of blue sensitivity.

In an attempt to use pyridine as condensing agent, the product was unsatisfactory, unchanged reagents being recovered.

[5-(3-*Ethylrhodanine*)][2-(4-*methyl*-3-*ethyl*-Δ^4-*thiazoline*][*β*-*methin*-5′-(3′-*ethylrhodanine*)]*dimethin*merocyanine.—4-Methyl-3-ethyl-2-dianilo*iso*propylidene-Δ^4-thiazoline (1·39 g.; 1 mol.), 3-ethylrhodanine (3 mols.), and pyridine (10 c.c.) were heated together at 130° for 3 minutes, and the reaction mixture was poured into water (150 c.c.). The resultant tar was induced to solidify by treatment with spirit and was crystallised from pyridine (10 c.c.), being obtained in 57% yield (Found: S, 33·35. $C_{19}H_{21}O_2N_3S_5$ requires S, 33·15%). The greyish blue crystals had m. p. 223° (decomp.). The narrow absorption curve had its maximum at 5720 A. and an inflexion at 5220 A. The *substance* considerably reduced the normal sensitivity of a photographic plate, whilst sensitising weakly to 6600 A. with the maximum at 6450 A.

With sodium acetate in acetic anhydride as condensing agent, in place of pyridine, the yield was substantially the same (54%).

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro-oxazole*)][2-(4-*methyl*-3-*ethyl*-Δ^4-*thiazoline*)][*β*-*methin*-5′-(4′-*keto*-2′-*thio*-3′-*ethyltetrahydro-oxazole*)]*dimethin*merocyanine.—4-Methyl-3-ethyl-2-dianilo*iso*propylidene-Δ^4-thiazoline (1·39 g.; 1 mol.), 4-keto-2-thio-3-ethyltetrahydro-oxazole (3 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (20 c.c.) were heated at 145—150° for 7 minutes, and the mixture poured into water. The tarry product was caused to solidify by means of spirit and was crystallised from methyl alcohol (60 c.c.), being obtained in 28% yield (Found: S, 21·35. $C_{19}H_{21}O_4N_3S_3$ requires S, 21·3%). The dark purple crystals had m. p. 189° (decomp.). The narrow absorption curve had its maximum at 5350 A. and an inflexion at 5000 A. The *compound* sensitised very weakly to 5700 A., the maximum being at 5400 A., and it considerably decreased the normal sensitivity.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzselenazoline*)][*β*-*methin*-5′-(3′-*ethylrhodanine*)]*dimethin*merocyanine.—This was similarly prepared from 3-ethyl-2-dianilo*iso*propylidenebenzselenazoline, 3-ethyl rhodanine, and sodium acetate in acetic anhydride, precipitated by ether, ground with water, and washed with spirit (88% yield). It was recrystallised from a mixture of ethyl alcohol and pyridine (16 c.c. of each per g.) and obtained in 75% yield. In this and other instances, nitrogen was determined by the method of Dumas (Found: N, 7·55. $C_{22}H_{21}O_2N_3S_4Se$ requires N, 7·4%). The dark green and gold crystals had m. p. 206° (decomp.). The broad absorption curve had its maximum at 5300 A. and an inflexion at 5700 A. To a photographic plate the *dye* imparted a trace of sensitisation, with the maximum about 5850 A., and decreased the normal blue sensitivity.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro-oxazole*)][2-(3-*ethylbenzselenazoline*)][*β*-*methin*-5′-(4′-*keto*-2′-*thio*-3′-*ethyltetrahydro-oxazole*)]*dimethin*merocyanine.—3-Ethylrhodanine in the preceding preparation was replaced by 4-keto-2-thio-3-ethyltetrahydro-oxazole and heating at 145—150° was for 15 minutes. After ether-precipitation and water-washing the product (61% yield) was boiled out with methyl alcohol (10 c.c. per g.) and recrystallised from a mixture of methyl alcohol and pyridine (15 c.c. of each per g.), giving a 48% yield (Found: N, 7·95. $C_{22}H_{21}O_4N_3S_3Se$ requires N, 7·85%). The scarlet crystals had m. p. 231° (decomp.). The broad absorption curve had its principal maximum at 5000 A., a slightly weaker one at 5150 A., and a shoulder at 5300 A. The *dye* reduced the normal sensitivity of a plate but caused extra-sensitivity to 6200 A. with the maximum at 5550 A.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro-oxazole*)][2-(3-*methylthiazolidine*)][*β*-*methin*-5′-(4′-*keto*-2′-*thio*-3′-*ethyltetrahydro-oxazole*)]*dimethin*merocyanine.—3-Methyl-2-dianilo*iso*propylidenethiazolidine (1·61 g.; 1 mol.), 4-keto-2-thio-3-ethyltetrahydro-oxazole (2·2 mols.), anhydrous sodium acetate (6 mols.), and acetic anhydride (8 c.c.) were heated together at 130—140° for 5 minutes. The solid was filtered off, washed (45% yield), and recrystallised from pyridine (5 c.c. per g.), resulting in 27% yield (Found: S, 22·3. $C_{17}H_{19}O_4N_3S_3$ requires S, 22·6%). The reddish-orange solid had m. p. about 229° with previous darkening and shrinking. Of two absorption maxima at 4455 and 5030 A., the former was the stronger. The *substance* strongly sensitised a gelatino-chloride photographic plate, with the maximum at 4500 A., sensitisation extending to 5700 A. for moderate exposures.

[4-(1-*Ethyldihydroquinoline*)][5-(3-*ethylrhodanine*)][*α*-*methin*-5′-(3′-*ethylrhodanine*)]*dimethin*merocyanine.—A mixture of crude 1-ethyl-4-dianilo*iso*propylidene-1:4-dihydroquinoline (1·89 g.; 1 mol.), 3-ethylrhodanine (3 mols.), anhydrous sodium acetate (8 mols.), and acetic anhydride (20 c.c.) was stirred at 140—150° for 2 minutes. The solid was filtered off, washed (24% yield), and recrystallised from pyridine and water (22 c.c. of each per g.), leaving a 21% yield (Found: S, 25·1. $C_{24}H_{23}O_2N_3S_4$ requires S, 25·0%). The dark blue crystals had m. p. about 285° (decomp.). The absorption maximum was at 5875 A. The *compound* did not sensitise and decreased the normal blue sensitivity of the plate.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzthiazoline*)]-*β*-*anilomethyldimethin*merocyanine (VII; X = S).—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (2 g.; 1 mol.), 3-ethylrhodanine (0·84 g.; 1 mol.), and pyridine (10 c.c.) were stirred together at 50—60° for 10 minutes. The solid precipitated by absolute ether (50 c.c.) (89% yield) was thrice boiled out with methyl alcohol (3 × 20 c.c.), leaving an 84% yield

(Found : S, 21·25. $C_{23}H_{21}ON_3S_3$ requires S, 21·3%). On recrystallisation from pyridine (9 c.c. per g.), the yield dropped to 60% (Found : S, 21·45%). The red crystals began to blacken at about 175°, were quite black and shrunken by 185°, and had m. p. about 195° (decomp.). A methyl-alcoholic solution was red at pH 6·0 and yellow at pH 5·3. One containing ammonia had its absorption maximum at 5230 A. and one containing sulphuric acid at 4400 A. The *dye* strongly sensitised a gelatino-chloride plate; the maximum was at 5750 A. and sensitisation extended to 6400 A.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro*-*oxazole*)][2-(3-*ethylbenzthiazoline*)]-β-*anilomethyldimethin*mero*cyanine* (VII; X = O).—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (3·83 g.; 1 mol.), 4-keto-2-thio-3-ethyltetrahydro-oxazole (2 mols.), and pyridine (20 c.c.) were stirred together at 50—63° for 30 minutes. The product precipitated by ether (200 c.c.) amounted to a 72% yield and, after boiling out with methyl alcohol (25 c.c.), a 71% yield remained (Found : S, 14·55. $C_{23}H_{21}O_2N_3S_2$ requires S, 14·75%). The red solid began to darken at about 195° and had m. p. at about 208° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 4975 A., and of one containing sulphuric acid at 4100 A. The *substance* sensitised a gelatino-chloride plate to 5400 A. with the maximum at 4800 A.

[5-(*Pyridinium* 3-*carboxymethylrhodanine*)][2-(3-*ethylbenzthiazoline*)]-β-*anilomethyldimethin*mero*cyanine*.—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (1·56 g.; 1 mol.), 3-carboxymethylrhodanine (1 mol.), and pyridine (20 c.c.) were heated together at 60—70° for 10 minutes, and the product precipitated with absolute ether. After being washed with water and with ether (1·87 g. left), it was boiled out with methyl alcohol (4 × 25 c.c.), and the residue was recrystallised from methyl alcohol (700 c.c.) (0·92 g. obtained), and again from methyl alcohol (500 c.c. per g.), giving a 22% yield (Found : S, 17·05. $C_{23}H_{19}O_3N_3S_3,C_5H_5N$ requires S, 17·15%). The flame-coloured crystals had m. p. 174° (decomp.). A methyl-alcoholic solution containing ammonia had its absorption maximum at 5055 A. with a secondary maximum at 4405 A.; one containing pyridine had maxima at 4325 A. and 5030 A., the former being the principal one. One containing sulphuric acid had its maximum at 4395 A. The *substance* sensitised a gelatino-chloride plate strongly to 6300 A. with the maximum at 5750 A.

[5-(1-*Phenyl*-3-*ethyl*-2-*thiohydantoin*)][2-(5-*chloro*-3-*ethylbenzthiazoline*)]-β-*anilomethyldimethin*mero*cyanine*.—5-Chloro-3-ethyl-2-dianilo*iso*propylidenebenzthiazoline (1·56 g.; 1 mol.), 1-phenyl-3-ethyl-2-thiohydantoin (3 mols.), and pyridine (15 c.c.) were heated together at 130—135° for 5 minutes. The product (2·81 g.), precipitated by water, was boiled out twice with methyl alcohol (40 c.c., 500 c.c.). The residue (1·35 g.) was taken up in hot acetic acid (3 c.c.) and precipitated by ether in 52% yield (Found : Cl, 6·25. $C_{29}H_{25}ON_4ClS_3$ requires Cl, 6·5%). The brick-red powder had m. p. 242—243° (decomp.), with shrinking from 137°. A methyl-alcoholic solution containing ammonia had the absorption maximum at 5110 A. and one containing sulphuric acid at 4300 A. The *compound* sensitised a gelatino-chloride emulsion to 6000 A. with the maximum at 5500 A.

[5-(2-*Diphenylamino*-4-*keto*-Δ^2-*thiazoline*)][2-(5-*chloro*-3-*ethylbenzthiazoline*)]-β-*anilomethyldimethin*mero*cyanine*.—This was prepared by heating 5-chloro-3-ethyl-2-dianilo*iso*propylidenebenzthiazoline (1·03 g.; 1 mol.), 2-diphenylamino-4-keto-Δ^2-thiazoline (3 mols.) and pyridine (10 c.c.) in a steam-bath for 9 hours. The precipitate obtained by ether was thrice boiled out with methyl alcohol (15 c.c., 2 × 25 c.c.) and, by recrystallising from pyridine (10 c.c.), obtained in 47% yield (Found : Cl, 6·3. $C_{33}H_{25}ON_4ClS_3$ requires Cl, 6·0%). The bright yellow powder had m. p. 247—248° (decomp.). A methyl-alcoholic solution containing ammonia had its absorption maximum at 4835 A. and one containing sulphuric acid at 4250 A. The *substance* sensitised a chloride plate to 5900 A. with the maximum at 5200 A.

[2-(4-*Methyl*-3-*ethyl*-Δ^4-*thiazoline*)][5-(3-*ethylrhodanine*)]-α-*anilomethyldimethin*mero*cyanine*.—4-Methyl-3-ethyl-2-dianilo*iso*propylidene-Δ^4-thiazoline (0·69 g.; 1 mol.), 3-ethylrhodanine (1·5 mols.), and absolute ethyl alcohol (7 c.c.) were boiled and stirred together for 2 minutes. After cooling, the dye was filtered off and washed (73% yield). On recrystallising from a mixture of ethyl alcohol (5 c.c.) and pyridine (2 c.c.), the yield was 65% (Found : S, 23·35. $C_{20}H_{21}ON_3S_3$ requires S, 23·15%). The crimson crystals had m. p. 182° (decomp.). A methyl-alcoholic solution was orange red at pH 7·8 and bright yellow at pH 6·8; one containing ammonia had its principal maximum at 4685 A., with a weaker one at 4830 A., and one containing sulphuric acid had the maximum at 4465 A. The *compound* sensitised a chloride plate to 6400 A. with the maximum at 5850 A.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro*-*oxazole*)][2-(4-*methyl*-3-*ethyl*-Δ^4-*thiazoline*)]-β-*anilomethyldimethin*mero*cyanine*.—4-Methyl-3-ethyl-2-dianilo*iso*propylidene-Δ^4-thiazoline (1·74 g.; 1 mol.), 4-keto-2-thio-3-ethyltetrahydro-oxazole (2·2 mols.), and pyridine (10 c.c.) were stirred together at 130° for 5 minutes and the resultant solution was poured into water. After decanting off the liquid, the residue was boiled out with ethyl alcohol (10 c.c.) and recrystallised from methyl alcohol (40 c.c.), giving a 47% yield (Found : S, 16·2. $C_{20}H_{21}O_2N_3S$ requires S, 16·05%). The bright orange crystals had m. p. 155° (decomp.). A methyl-alcoholic solution containing ammonia had its absorption maximum at 4510 A. and one containing sulphuric acid at 4150 A. The *compound* sensitised a chloride plate weakly up to 5700 A., the maximum lying at 5200 A.; the normal blue sensitivity was decreased.

[5-(1-*Phenyl*-3-*ethyl*-2-*thiohydantoin*)][2-(4-*methyl*-3-*ethyl*-Δ^4-*thiazoline*)]-β-*anilomethyldimethin*mero*cyanine*.—4-Methyl-3-ethyl-2-dianilo*iso*propylidene-Δ^4-thiazoline (3·47 g.; 1 mol.), 1-phenyl-3-ethyl-2-thiohydantoin (1·5 mols.), and ethyl alcohol (20 c.c.) were boiled together with stirring for 3 minutes. The *dye* was filtered off and boiled out twice with methyl alcohol (2 × 75 c.c.), the residue amounting to a 92% yield (Found : S, 13·3. $C_{16}H_{16}ON_4S_2$ requires S, 13·5%). A preparation similarly carried out in boiling pyridine for 4 minutes was poured into water and the crude dye was boiled out with methyl alcohol (30 c.c.) and recrystallised from pyridine (15 c.c.), giving a 68% yield (Found : S, 13·35%). The maroon and gold crystals had m. p. 222° (decomp.). Their methyl-alcoholic solution was orange red at pH 8·4 and bright yellow at pH 6·8. One containing ammonia had its absorption maximum at 4860 A., and one containing sulphuric acid at 4470 A. The dye sensitised a chloride emulsion very weakly with the maximum at 4850 A., sensitisation extending to 5200 A.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzselenazoline*)]-β-*anilomethyldimethin*mero*cyanine*.—3-Ethyl-2-dianilo*iso*propylidenebenzselenazoline (0·86 g.; 1 mol.), 3-ethylrhodanine (3 mols.), and pyridine (5 c.c.) were heated together at 120° for 3 minutes. The precipitate (0·91 g.) obtained with ether was recrystallised from a mixture of pyridine (10 c.c.) and methyl alcohol (10 c.c.) and resulted in 80% yield (Found :

N, 8·55. $C_{22}H_{21}ON_3S_2Se$ requires N, 8·45%). The lustrous vermilion crystals had m. p. 197° (decomp.). A methyl-alcoholic solution was pink at pH 4·6 and bright yellow at pH 3·9. One containing ammonia had its absorption maximum at 5100 A., and one containing sulphuric acid at 4400 A., with an inflexion to the curve at 4540 A. The *compound* sensitised a washed chloride plate fairly strongly, the maximum lying at 5700 A. and sensitisation extending to 6300 A.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro*-*oxazole*)][2-(3-*ethylbenzselenazoline*)]-β-*anilomethyldimethin*mero*cyanine*.—This was similarly prepared but with 4-keto-2-thio-3-ethyltetrahydro-oxazole in place of 3-ethylrhodanine and heating was for 5 minutes. The product (62% yield) precipitated by ether was recrystallised from a mixture of ethyl alcohol and pyridine (13 c.c. of each per g.) and gave a 47% yield (Found: N, 8·9. $C_{23}H_{21}O_2N_3SSe$ requires N, 8·7%). The bright orange crystals had m. p. 161° (decomp.). A methyl-alcoholic solution containing ammonia had its absorption maximum at 4850 A. and one containing sulphuric acid at 4105 A. The *dye* sensitised a chloride plate to 5900 A., with the maximum at 5400 A.

[5-(1-*Phenyl*-3-*ethyl*-2-*thiohydantoin*)][2-(3-*ethylbenzselenazoline*)]-β-*anilomethyldimethin*mero*cyanine*.—This was similarly prepared but with 1-phenyl-3-ethyl-2-thiohydantoin (2·64 g.; 3 mols.) as the compound with reactive methylene, and was precipitated by water. The product was boiled out with methyl alcohol (30 c.c.) and the residue crystallised from pyridine (20 c.c.), giving a 32% yield (Found: N, 10·2. $C_{29}H_{26}ON_4SSe$ requires N, 10·05%). The brick-red crystals had a gold reflex and melted at 236° (decomp.). A methyl-alcoholic solution containing ammonia had its absorption maximum at 5055 A., and one containing sulphuric acid at 4290 A. The *substance* sensitised a chloride plate strongly, the maximum lying at 5600 A. and sensitisation extending to 6150 A.

[2-(3-*Ethylthiazolidine*)][5-(3-*ethylrhodanine*)]-α-*anilomethyldimethin*mero*cyanine*.—3-Ethyl-2-dianilo-*iso*propylidenethiazolidine (0·84 g.; 1 mol.) and 3-ethylrhodanine (1 mol.) were suspended in ethyl alcohol (30 c.c.) at 0° and kept thus for 15 minutes, with thorough stirring. The solid was filtered off, washed (0·88 g. left), and recrystallised from a mixture of ethyl alcohol and pyridine (10 c.c. of each), being obtained in 66% yield (Found: S, 23·65. $C_{19}H_{21}ON_3S_3$ requires S, 23·85%). The orange crystals had m. p. 172° (decomp.). A methyl-alcoholic solution containing pyridine had its absorption maximum at 4825 A., and one containing sulphuric acid at 4410 A. The *substance* sensitised a chloride plate strongly from 4600 to 5800 A., with the maximum at 5350 A.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro*-*oxazole*)][2-(3-*ethylthiazolidine*)]-β-*anilomethyldimethin*mero*cyanine*.—3-Ethyl-2-dianilo*iso*propylidenethiazolidine (1·68 g.; 1 mol.), 4-keto-2-thio-3-ethyltetrahydro-oxazole (1 mol.), and alcohol (40 c.c.) were mixed and kept at 0° for 1 hour. After water-washing, the product (1·4 g.) was recrystallised from a mixture of ethyl alcohol (10 c.c.) and pyridine (5 c.c.), giving a 60% yield (Found: S, 16·75. $C_{19}H_{21}O_2N_3S_3$ requires S, 16·55%). The orange crystals had m. p. 139° (decomp.). A methyl-alcoholic solution containing pyridine had a broad absorption curve with its maximum at 4370 A., whilst one containing sulphuric acid had a curve with a sharp peak at 4110 A. On a chloride plate the *substance* conferred slight extra-sensitivity extending to 4500 A.

[2-(3-*Ethylthiazolidine*)][5-(2-*diphenylamino*-4-*keto*-Δ^2-*thiazoline*)]-α-*anilomethyldimethin*mero*cyanine*.—3-Ethyl-2-dianil*iso*propylidenethiazolidine (1·68 g.; 1 mol.), 2-diphenylamino-4-keto-Δ^2-thiazoline (1 mol.), and ethyl alcohol (40 c.c.) were boiled and stirred together for 5 minutes. The washed product (2·03 g.) was recrystallised from a mixture of ethyl alcohol (10 c.c.) and pyridine (18 c.c.) and obtained in 74% yield (Found: S, 12·45. $C_{29}H_{26}ON_4S_2$ requires S, 12·55%). The deep yellow crystals had m. p. 209° (decomp.). A methyl-alcoholic solution containing ammonia had its absorption maximum at 4380 A. and one containing sulphuric acid at 3990 A. The *compound* strongly sensitised a chloride plate, the maximum lying at 5000 A. and sensitisation extending to 5500 A.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro*-*oxazole*)][2-(3-*ethylbenzthiazoline*)][β-*methin*-5′-(3′-*ethylrhodanine*)]-*dimethin*mero*cyanine* (XII).—[5-(4-Keto-2-thio-3-ethyltetrahydro-oxazole)][2-(3-ethylbenzthiazoline)]-β-anilomethyldimethin*mero*cyanine (VII; X = O) (0·87 g.; 1 mol.), 3-ethylrhodanine (1 mol.), anhydrous sodium acetate (4 mols.), and acetic anhydride (8 c.c.) were stirred together at 130—140° for 6 minutes. After cooling, the solids were filtered off and washed successively with acetic anhydride, ether, and water. The residue (0·76 g.) was dissolved in hot pyridine (15 c.c.) and precipitated with absolute ether (55 c.c.), giving a 58% yield (Found: S, 25·55. $C_{22}H_{21}O_3N_3S_4$ requires S, 25·5%). The maroon solid had no definite m. p. but melting and decomposition took place from 215° to 270°. The absorption maximum was at 5475 A. The *substance* decreased the normal sensitivity of a plate whilst sensitising weakly from 5600 to 6000 A.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro*-*oxazole*)][2-(4-*methyl*-3-*ethyl*-Δ^4-*thiazoline*)][β-*methin*-5′-(3′-*ethylrhodanine*)]*dimethin*mero*cyanine*.—This was prepared by heating together [2-(4-methyl-3-ethyl-Δ^4-thiazoline)][5-(3-ethylrhodanine)]-α-anilomethyldimethin*mero*cyanine (1·04 g.; 1 mol.), 4-keto-2-thio-3-ethyltetrahydro-oxazole (2 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (25 c.c.) at 145—150° for 7 minutes. The reaction mixture was poured into water. After decantation of the cooled liquid, crystallisation of the residue was effected by stirring with spirit; it was recrystallised from methyl alcohol (70 c.c.) and obtained in 65% yield (Found: S, 27·6. $C_{19}H_{21}O_3N_3S_4$ requires S, 27·4%). The purple crystals had m. p. 215° (decomp.). The narrow absorption curve had its maximum at 5545 A. The *compound* strongly sensitised a gelatino-chloride plate, sensitisation extending to 6500 A. and the maximum lying at 5500 A.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro*-*oxazole*)][2-(3-*ethylbenzselenazoline*)][β-*methin*-5′-(3′-*ethylrhodanine*)]-*dimethin*mero*cyanine*.—[5-(3-Ethylrhodanine)][2-(3-ethylbenzselenazoline)]-β-anilomethyldimethin-*mero*cyanine (1·00 g.; 1 mol.), 4-keto-2-thio-3-ethyltetrahydro-oxazole (2 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (30 c.c.) were heated together at 150° for 15 minutes, and the reaction mixture poured into water. The resultant solid was washed with ether and recrystallised from methyl alcohol (100 c.c.), being obtained in 56% yield (Found: N, 7·6. $C_{22}H_{21}O_3N_3S_3Se$ requires N, 7·65%). The dark purple crystals had m. p. 135° (decomp.). The broad absorption curve had its maximum at 5190 A. The *substance* sensitised a chloride plate to 6200 A. with maxima at 4900 A. and 5750 A.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzthiazoline*)][ββ′-*dimethin*-2′-(1′-*ethylquinolinium iodide*)]*dimethin*-mero*cyanine* (XIII).—[5-(3-Ethylrhodanine)][2-(3-ethylbenzthiazoline)]-β-anilomethyldimethin*mero*-

cyanine (VII; X = S) (0·45 g.; 1 mol.), quinaldine ethiodide (1 mol.), anhydrous sodium acetate (4 mols.), and acetic anhydride (20 c.c.) were stirred together at 140—150° for 5 minutes. The solid was filtered off, washed with ether, and ground with water (15 c.c.). The residue (0·41 g.) was recrystallised from methyl alcohol (225 c.c.) and gave a 47% yield (Found: I, 19·2. $C_{29}H_{33}ON_3IS_3$ requires I, 19·3%). The dark bronze crystals had m. p. 244° (decomp.). The absorption maximum was at 6080 A. The *substance* considerably desensitised a photographic plate and did not confer extra-sensitivity.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzthiazoline*)][*ββ'-dimethin*-2'-(3'-*ethylbenzthiazolium iodide*)]*dimethin*mero*cyanine* (XV).—Bis-2-(3-ethylbenzthiazole)-α-anilomethyltrimethincyanine iodide (XIV) (1·20 g.; 1 mol.), 3-ethylrhodanine (2 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (20 c.c.) were heated together at 140—150° for 10 minutes. The washed product (0·98 g.) was boiled out with, and recrystallised from, methyl alcohol (27 c.c., 150 c.c.), giving a 38% yield (Found: I, 18·85. $C_{27}H_{26}ON_3IS_4$ requires I, 19·15%). The bronze powder had m. p. 227° (decomp.). The absorption maximum was at 5750 A. The *compound* showed photographic desensitising power and did not sensitise.

[5-(3-*Ethylrhodanine*)][2-(4-*methyl*-3-*ethyl*-Δ^4-*thiazoline*)][*ββ'-dimethin*-2'-(3'-*ethylbenzthiazolium iodide*)]*dimethin*mero*cyanine*.—[5-(3-Ethylrhodanine)][2-(4-methyl-3-ethyl-Δ^4-thiazoline)]-β-anilomethyldimethin*mero*cyanine (0·83 g.; 1 mol.), 2-methylbenzthiazole ethiodide (2 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (25 c.c.) were stirred together at 145—150° for three minutes. Ether-precipitation was carried out and the solid washed with warm water and boiled out with methyl alcohol (20 c.c.). On recrystallising the residue from acetic acid (200 c.c.), the yield was 76% (Found: I, 20·4. $C_{24}H_{26}ON_3IS_4$ requires I, 20·2%). The emerald-green crystals had m. p. 240° (decomp.). The absorption curve had its maximum at 5750 A. and an inflexion at 5300 A. The *dye* did not sensitise and decreased the normal blue sensitivity of the plate.

[5-(3-*Ethylrhodanine*)][2-(4-*methyl*-3-*ethyl*-Δ^4-*thiazoline*)][*ββ'-dimethin*-2'-(3'-*ethyl*-6' : 7'-*benzbenzthiazolium iodide*)]*dimethin*mero*cyanine*.—This was similarly prepared but from 2-methyl-6 : 7-benzbenzthiazole ethiodide instead of from 2-methylbenzthiazole ethiodide. After being washed with hot water, the residue (1·37 g.) was recrystallised from methyl alcohol (535 c.c.) and gave a 76% yield (Found: I, 18·9. $C_{28}H_{28}ON_3IS_4$ requires I, 18·75%). The brilliant green crystals had m. p. 260° (decomp.). The narrow absorption curve had its maximum at 5945 A. and an inflexion at 5500 A. The *dye* decreased the normal blue sensitivity of a plate without conferring extra-sensitivity.

[5-(3-*Ethylrhodanine*)][2-(4-*methyl*-3-*ethyl*-Δ^4-*thiazoline*)][*ββ'-dimethin*-2'-(3'-*ethyl*-Δ^2-*thiazolinium iodide*)]*dimethin*mero*cyanine* (XVII).—[2-(3-Ethyl-Δ^2-thiazoline)][2-(4-methyl-3-ethylthiazole)]-γ-anilomethyltrimethincyanine iodide (1·02 g.; 1 mol.), 3-ethylrhodanine (1·5 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (15 c.c.) were stirred together at 140—150° for 5 minutes. Ether-precipitation was effected, followed by washing with water, and the residue, on recrystallisation from methyl alcohol (25 c.c.), gave a 58% yield (Found: I, 21·75. $C_{20}H_{25}ON_3IS_4$ requires I, 21·9%). The purple crystals had m. p. 214° (decomp.). The absorption curve had its maximum at 5360 A. and an inflexion at 5000 A. The *substance* sensitised weakly to 6200 A., the maximum lying at 5900 A., but considerably diminished the normal sensitivity.

[5-(1-*Phenyl*-3-*ethyl*-2-*thiohydantoin*)][2-(4-*methyl*-3-*ethyl*-Δ^4-*thiazoline*)][*ββ'-dimethin*-2'-(3'-*ethylbenzthiazolium iodide*)]*dimethin*mero*cyanine* (XVI).—[5-(1-Phenyl-3-ethyl-2-thiohydantoin)][2-(4-methyl-3-ethyl-Δ^4-thiazoline)]-β-anilomethyldimethin*mero*cyanine (1·19 g.; 1 mol.), 2-methylbenzthiazole ethiodide (2 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (30 c.c.) were stirred together at 145—150° for 5 minutes. The product was precipitated with ether and washed with warm water; after boiling out with, and recrystallising from, methyl alcohol (10 c.c., 60 c.c.), the yield was 31% (Found: I, 18·5. $C_{30}H_{31}ON_4IS_3$ requires I, 18·5%). The dark green crystals had m. p. 225° (decomp.). The broad absorption curve had its maximum at 5765 A. and an inflexion at 5400 A. The *substance* depressed the sensitivity of a photographic plate.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzselenazoline*)][*ββ'-dimethin*-2'-(3'-*ethylbenzthiazolium iodide*)]*dimethin*mero*cyanine* (XVIII; X=S).—[5-(3-Ethylrhodanine)][2-(3-ethylbenzselenazoline)]-β-anilomethyldimethin*mero*cyanine (0·50 g.; 1 mol.), 2-methylbenzthiazole ethiodide (2 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (15 c.c.) were stirred together at 145—150° for 3 minutes. The product was precipitated with ether, washed with water (84% yield left), and recrystallised from methyl alcohol (600 c.c. per g.), whereupon the yield was 71% (Found: I, 18·0. $C_{27}H_{28}ON_3IS_3Se$ requires I, 17·85%). The dark purple crystals had m. p. 235° (decomp.). The broad absorption curve had its maximum at 5800 A. and an inflexion at 5410 A. The *dye* strongly depressed the normal sensitivity of a plate and did not confer extra-sensitivity.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzselenazoline*)][*ββ'-dimethin*-2'-(3'-*ethyl*-6' : 7'-*benzbenzthiazolium iodide*)]*dimethin*mero*cyanine*.—This was similarly prepared but 2-methyl-6 : 7-benzbenzthiazole ethiodide took the place of 2-methylbenzthiazole ethiodide. The ether-precipitated, water-washed dye was boiled out with, and recrystallised from, methyl alcohol (15 c.c., 300 c.c.), the hot filtrate being concentrated to ¼ volume to give a 43% yield (Found: I, 16·7. $C_{31}H_{28}ON_3IS_3Se$ requires I, 16·7%). The blue-green crystals had m. p. 240° (decomp.). The broad absorption curve had its maximum at 5930 A. and an inflexion at 5300 A. The *dye* decreased the blue sensitivity and did not confer extra-sensitivity.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzselenazoline*)][*ββ'-dimethin*-2'-(3'-*ethylbenzselenazolium iodide*)]*dimethin*mero*cyanine* (XVIII; X = Se).—This was similarly prepared but the quaternary salt was 2-methylbenzselenazole ethiodide. The precipitated, washed solid (0·65 g.) was recrystallised from methyl alcohol (550 c.c.) and gave a 71% yield (Found: I, 16·8. $C_{27}H_{28}ON_3IS_3Se_2$ requires I, 16·75%). The dark purple crystals had m. p. 245° (decomp.). The broad absorption curve had its maximum at 5820 A. and an inflexion at 5400 A. There was no sensitisation but very strong desensitisation.

Our thanks are due to our colleagues Dr. L. G. S. Brooker and Mr. F. L. White for absorption data concerning eight dyes, Miss M. D. Gauntlett and Mrs. B. Inman for absorption measurements, Dr. B. H. Carroll and Mr. J. Morgan for sensitising tests, and Mr. V. E. Lead for pH measurements.

KODAK LTD., WEALDSTONE, HARROW, MIDDLESEX. [*Received, October 21st*, 1948.]

238. *A Trimethincyanine; a Trimethinoxonol and Some Compounds related to Trimethinoxonols; Some Di- and Tetra-methin*merocyanines.

By Frances M. Hamer and Barbara S. Winton.

A trimethincyanine and a trimethinoxonol are described, also five anilinoallylidene compounds, intermediate in structure to oxonols, and three corresponding acetanilido-derivatives. Seven dimethin*mero*cyanines and five tetramethin*mero*cyanines are also described. Absorption maxima of methyl-alcoholic solutions are recorded, those of the anilinoallylidene compounds being of acidified and basified solutions.

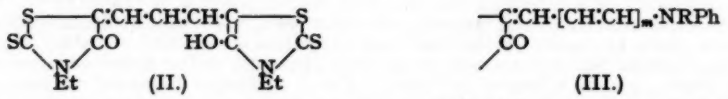
Neocyanines, the first trinuclear dyes which we synthesised, were shown to be structurally related to tri- and penta-methincyanines, and the absorption maximum of each was compared with those of one or two dyes of the former class and one of the latter (Hamer, Rathbone, and Winton, *J.*, 1947, 1434; 1948, 1872). Subsequently, trinuclear dyes of a new type were synthesised, each of which was correlated with one trimethinoxonol and with one or two dimethin*mero*cyanines; with trinuclear dyes of yet another type, each was related to a trimethincyanine and to a di- and a tetra-methin*mero*cyanine (*idem*, this vol., p. 1113). The preparations of a trimethincyanine, of these dinuclear *mero*cyanines, of a trimethinoxonol, and of substances structurally related to trimethinoxonols, form the subject of the present paper.

" Oxonol " is a useful trivial name introduced by Brooker, and may conveniently be included in the systematic nomenclature. Oxonols are characterised by possessing two cyclic nuclei, linked by an odd-numbered methin chain, comprising structure (I). Symmetrical methinoxonols

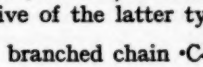
(I*a*.) (I*b*.)

(I; $m = 0$), containing two phenylmethylpyrazolone residues, were described many years ago (Knorr, *Annalen*, 1887, **238**, 137; Stolz, *J. pr. Chem.*, 1897, **55**, 145; Claisen, *Annalen*, 1897, **297**, 1), as also such compounds having two ketodihydrothionaphthen nuclei (Friedländer and Kielbasinski, *Ber.*, 1911, **44**, 3098; Friedländer and Risse, *Ber.*, 1914, **47**, 1919). In the patent literature there is disclosed the use of certain symmetrical methinoxonols and tri-, penta-, and hepta-methinoxonols (I; $m = 0$, 1, 2, or 3) as photographic filter dyes (Gaspar, B.P. 506,385/1937). More recent scientific literature contains an account of one series of oxonols in which two 3-ketodihydrothionaphthen nuclei are linked by methin, trimethin, and pentamethin chains, respectively (Sveschnikov and Levkoev, *J. Gen. Chem. Russia*, 1940, **10**, 274).

Of one desired unsymmetrical, and four symmetrical, oxonols it was only found possible to prepare (II), which was obtained by condensing 3-ethylrhodanine with β-anilinoacraldehyde anil hydrochloride, in the presence of triethylamine in alcohol. The intense blue of its ammoniacal salt changed to red on acidification.



(II.) (III.)

By condensing a cyclic compound having a reactive ketomethylene group with suitable anils, compounds intermediate in structure to oxonols and comprising the skeleton (III) may be prepared. Compounds of this kind having one methin group (III; $m = 0$) were discovered earliest (Dains and Brown, *J. Amer. Chem. Soc.*, 1909, **31**, 1148; Dains, Thompson, and Asendorf, *ibid.*, 1922, **44**, 2310), and those with a trimethin chain (III; $m = 1$) have been described in the patent literature (Kodak Ltd., B.P. 470,725/1935). Five of the latter type have now been prepared, for comparison with intermediates having the branched chain  which were used in preparing trinuclear dyes (Hamer, Rathbone, and Winton, this vol., p. 1113).

(IV.) (V.)

These are (IV; R = Et, X = O, S, or NPh, respectively; R = $CH_2 \cdot CO_2H$, X = S) and (V), the first three of which are examples in the patent. With dye (IV; X = S), having the

$CH_2{\cdot}CO_2H$ group, and with dye (V) having the NPh_2 group, the absorption maxima of methyl-alcoholic solutions containing sulphuric acid lay at wave-lengths longer by 55 A. and 225 A., respectively, than did those of the corresponding methyl-alcoholic solutions containing ammonia. With the other three compounds represented by (IV), the addition of acid or alkali to the methyl-alcoholic solution did not affect the position of the absorption maximum. In the case of three *acetyl* derivatives of (IV; R = Et, X = O, S, or NPh, respectively), the absorption maxima lay at wave-lengths shorter (by 500—695 A.) than did those of the corresponding anilino-compounds themselves, as recorded also for pairs of acetanilido- and anilino-compounds which are cyanine intermediates (Brooker, White, Keyes, Smyth, and Oesper, *J. Amer. Chem. Soc.*, 1941, **63**, 3192).

Intermediate between the oxonols, with structure (I), and the cyanines, in which two heterocyclic nitrogen-containing nuclei are linked by an odd-numbered methin chain comprising structure (VI; $m = 0, 1, 2, 3$, etc.; n and $n' = 0$ or 1), is another class of dye, which was discovered independently by Kendall (B.P. 426,718/1933) and by Brooker (Kodak Ltd., B.P.

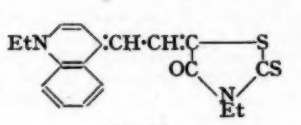
(VI*a*.) $NR[{\cdot}CH{:}CH]_n{\cdot}C{:}CH[{\cdot}CH{:}CH]_m{\cdot}C[{:}CH{\cdot}CH]_{n'}{:}N^+R'\ X^-$

$\Downarrow\Uparrow$

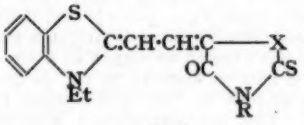
(VI*b*.) $X^-\ {}^+NR[{:}CH{\cdot}CH]_n{:}C{\cdot}CH[{:}CH{\cdot}CH]_m{:}C[{\cdot}CH{:}CH]_{n'}{\cdot}NR'$

450,958/1934). They comprise structure (VII; $m = 0, 1, 2, 3$; $n = 0$ or 1), in which an even-numbered methin chain links a heterocyclic nitrogen-containing nucleus to a cyclic ketomethylene residue. For these non-ionic compounds, which are prepared from cyanine intermediates, one of us (F. M. H.) suggested the term *mero*cyanine (μερος = part) and this has proved acceptable as a general term (Levkoev, Sveschnikov, and Durmaschkina, *J. Gen. Chem. Russia*, 1940, **10**, 773; Brooker, White, Keyes, Smyth, and Oesper, *loc. cit.*; Stammers and I.C.I. Ltd., B.P. 587,481/1944). Its inclusion in the systematic nomenclature is now required, in order to name our new types of trinuclear dyes (Hamer, Rathbone, and Winton, this vol., p. 1113). In naming *mero*cyanines it seemed logical to follow the pattern of the simplified names used for cyanine dye bases, as suggested by Dr. J. T. Hewitt, F.R.S. (Hamer, *J.*, 1940, 799), rather than that of the systematic names used for the cyanines themselves (Fisher and Hamer, *J.*, 1937, 907; Beilenson and Hamer, *J.*, 1942, 98).

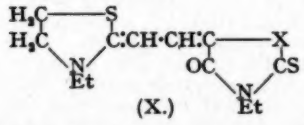
(VII.) $NR[{\cdot}CH{:}CH]_n{\cdot}C[{:}CH{\cdot}CH]_m{:}C{\cdot}CO$



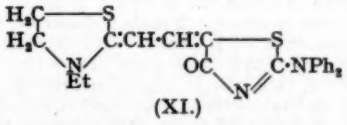
(VIII.)



(IX.)



(X.)

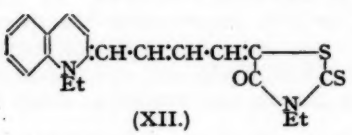


(XI.)

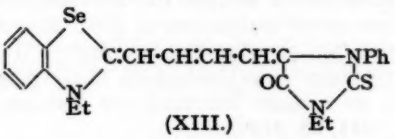
Eight *dimethin*mero*cyanines* were made, namely (VIII), (IX; R = Et, X = O; R = Et, X = S; R = $CH_2{\cdot}CO_2H$, X = S), the 5-chloro-derivative of (IX; R = Et, X = S), (X; X = O or S), and (XI). Six of these dyes were prepared from the appropriate β-acetanilidovinyl quaternary salt, whilst (X; X = S) was prepared from a β-anilinovinyl salt, and the 5-chloro-derivative of (IX; R = Et, X = S) was prepared by condensing a quaternary salt having a reactive methyl group with an acetanilidoallylidene compound (III; $m = 1$, R = Ac).

Five *tetramethin*mero*cyanines* were prepared, namely (XII), (XIII), and the higher vinylene homologues of (IX; N = Et; X = S and NPh, respectively), and of (X; X = S). The preparation of eleven tetramethin*mero*cyanines is given in the patent literature (Kodak Ltd., B.P. 450,958/1934), where the appropriate acetanilidobutadienyl salt was condensed with the heterocyclic methylene compound, by means of triethylamine in alcohol, one dye thus prepared being the higher vinylene homologue of (IX; X = S). In view of the observed instability of

these acetanilido-compounds (Hamer, *J.*, 1949, 32), our method consisted in using triethylamine in acetic anhydride as condensing agent, the starting point being the anilinobutadienyl salt. Each tetramethin*mero*cyanine was liable to be accompanied by the corresponding pentamethincyanine, which in two instances was present in considerable amount; the types could, however,



(XII.)



(XIII.)

be separated by benzene, in which only the former is soluble. The higher vinylene homologue of (X; X = S) was accompanied by a by-product, having about its own solubility in various organic solvents; the latter was left undissolved when the *tetramethin*mero*cyanine* was taken up by hydrochloric acid and was identified as the acetyl derivative of (IV; R = Et, X = S). The process whereby this 3-ethyl-5-(γ-acetanilidoallylidene)rhodanine is formed from 3-ethylrhodanine with 2-(4′-anilino-1′ : 3′-butadienyl)-Δ²-thiazoline ethiodide and triethylamine in acetic anhydride is obscure. The compounds comprise photographic sensitisers. Tests were carried out on gelatino-bromide plates except where otherwise stated.

Experimental.

[2-(4-*Methyl*-3-*ethyl*thiazole)][2-(3-*ethyl*-6 : 7-*benzbenz*thiazole)]*trimethincyanine Iodide.*—4-Methyl-2-β-acetanilidovinylthiazole ethiodide (2·07 g.; 1 mol.) and 2-methyl-6 : 7-benzbenzthiazole ethiodide (1 mol.) were mixed with ice-cold alcohol (45 c.c.) and triethylamine (2·2 mols.) and kept at 0° for 5 days. The washed cyanine (2·47 g.) was twice boiled out with methyl alcohol (2 × 20 c.c.). The solids which crystallised (0·16 + 0·17 g.) were added to the residue (1·86 g.), and the whole recrystallised from methyl alcohol (200 c.c.), giving a 72% yield. After a second recrystallisation (100 c.c. per g.), the yield of *iodide* was 63% (Found: I, 24·95. $C_{33}H_{33}N_3IS_3$ requires I, 25·05%). The dark green crystals had no definite m. p.; shrinking began at about 180° and violent decomposition occurred between 230° and 240°. The absorption maximum was at 5660 A. Sensitisation was from 4500 to 6500 A. with a maximum at 5900 A.

Bis-[5-(3-*ethyl*rhodanine)]*trimethinoxonol* (II).—A mixture of β-anilinoacraldehyde anil hydrochloride (5·17 g.; 1 mol.), 3-ethylrhodanine (4 mols.), absolute alcohol (40 c.c.), and triethylamine (2 mols.) was boiled under reflux for 6 hours. The reaction mixture was cooled, filtered to remove any by-product, and the filtrate shaken with aqueous ammonia (*d* 0·885; 400 c.c.) which had been saturated with ammonium chloride, and with benzene (800 c.c.). At first both layers were blue but after standing for a few days they lost this colour, the ammonium salt of the dye separating as a tar, which subsequently hardened. It was filtered off and washed with benzene. To free it from ammonium chloride, it was thrice extracted with acetone (3 × 20 c.c.). Evaporation of the solvent from the deep blue extract left the bronze ammonium salt (2·99 g.). The salt was ground with aqueous ammonia (5 c.c., *d* 0·965, per g.), and the mixture added to boiling water (400 c.c. per g.); the hot filtrate was treated with concentrated hydrochloric acid (8 c.c. per g.), and the precipitated *oxonol* was filtered off and washed, being obtained in 12% yield (Found, after drying in a vacuum at 60—80°: S, 35·55. $C_{13}H_{14}O_2N_2S_4$ requires S, 35·8%). The black solid began to shrink at about 160° and gradually decomposed, resulting in a brown drop by 210°, but it had no definite m. p. A methyl-alcoholic solution containing ammonia had its absorption maximum at 6100 A. On acidification the colour changed from blue to red but this red soon faded to yellowish. The dye desensitised, without sensitising, and gave chemical fog.

4-*Keto*-2-*thio*-3-*ethyl*-5-(γ-*anilinoallylidene*)*tetrahydro-oxazole* (IV; R = Et, X = O).—4-Keto-2-thio-3-ethyltetrahydro-oxazole (0·72 g.; 2 mols.), β-anilinoacraldehyde anil hydrochloride (0·65 g.; 1 mol.), and piperidine (0·50 c.c.; 2 mols.), dissolved in absolute ethyl alcohol (100 c.c.), were allowed to react at room temperature for 18 hours. The crystals were filtered off and washed (61% yield). After recrystallisation from pyridine (9 c.c.) and water (4·5 c.c.), the yield was 54% (Found, after drying in a vacuum at 60—80°: S, 11·8. $C_{14}H_{14}O_2N_2S$ requires S, 11·7%). The deep orange crystals had m. p. 244° (decomp.). Whether a methyl-alcoholic solution contained ammonia or sulphuric acid, the absorption maximum was at 4460 A., the curve for the acid solution being more rounded than the other. The *dye* sensitised a gelatino-chloride plate to 6100 A., with the maximum at 5200 A. (cf. examples 3 and 6 of B.P. 470,725).

4-*Keto*-2-*thio*-3-*ethyl*-5-(γ-*acetanilidoallylidene*)*tetrahydro-oxazole.*—The foregoing compound (1·62 g.; 1 mol.), acetic anhydride (8 c.c.), and triethylamine (1 mol.) were boiled together under reflux for 5 minutes, as in B.P. 470,725, example 6. The washed product (1·70 g.) was twice recrystallised from acetic acid (18 c.c. per g.) and obtained in 67% yield. The *acetyl* derivative was dried in a vacuum at 80—100° and analysed by the method of Carius, which procedure was adopted throughout this work, except where otherwise stated (Found: S, 10·15. $C_{16}H_{16}O_3N_2S$ requires S, 10·15%). The pale yellow crystals had m. p. 240° with previous softening; in the patent, 247—249° (decomp.) is given. The absorption maximum was at 3775 A. The substance sensitised a gelatino-chloride plate to 5000 A. with the maximum at 4100 A.

3-*Ethyl*-5-(γ-*anilinoallylidene*)*rhodanine* (IV; R = Et, X = S).—3-Ethylrhodanine (1·61 g.; 1 mol.), β-anilinoacraldehyde anil hydrochloride (1 mol.), triethylamine (1 mol.), and absolute alcohol (20 c.c.) were boiled together for 2 minutes. The washed crystals (78% yield) were recrystallised from methyl alcohol (250 c.c. per g.). The 60% yield fell to 57% on a second recrystallisation from methyl alcohol with charcoal (0·2 g. per g.) (Found: S, 22·35. $C_{14}H_{14}ON_2S_2$ requires S, 22·1%). The red crystals

melted at 207°. A methyl-alcoholic solution containing ammonia had its absorption maximum at 4775 A. and one containing sulphuric acid at 4795 A. The *rhodanine* sensitised a chloride plate to 6100 A. with the maximum at 5400 A. and with some decrease of the original blue sensitivity (cf. example 2 of B.P. 470,725).

3-*Ethyl*-5-(*γ-acetanilidoallylidene*)*rhodanine*.—3-Ethyl-5-(γ-anilinoallylidene)rhodanine was acetylated with acetic anhydride and triethylamine, as in B.P. 470,725. The washed crystals, after recrystallisation from pyridine (10 c.c. per g.), gave a 77% yield (Found: S, 19·4. $C_{16}H_{16}O_2N_2S_2$ requires S, 19·3%). The yellow crystals deepened in colour from 170° and had m. p. 222·5°. The m. p. recorded in the patent is 225·5—226·5°. The absorption maximum was at 4115 A. The *acetyl* derivative decreased the blue sensitivity of a gelatino-chloride plate and sensitised weakly from 4400 to 5400 A., with the maximum at 4900 A.

1-*Phenyl*-3-*ethyl*-5-(*γ-anilinoallylidene*)-2-*thiohydantoin* (V; R = Et, X = NPh.).—As in example 8 of B.P. 470,725, equimolecular quantities of 1-phenyl-3-ethyl-2-thiohydantoin (2·20 g.), β-anilinoacraldehyde anil hydrochloride, and triethylamine, in absolute alcohol (15 c.c.), were boiled together for 30 minutes. The washed product (77% yield) was recrystallised from pyridine (10 c.c.) and water (5 c.c.), giving a 60% yield (Found, after drying in a vacuum at 60—80°: S, 9·1. $C_{20}H_{19}ON_3S$ requires S, 9·2%). The bluish-red crystals had m. p. 128—130° (decomp.). A methyl-alcoholic solution, whether containing ammonia or sulphuric acid, had its maximum at 4650 A., but the acid one faded during exposure. The *dye* sensitised a chloride plate to 6000 A., the maximum lying at 5350 A.

1-*Phenyl*-3-*ethyl*-5-(*γ-acetanilidoallylidene*)-2-*thiohydantoin*.—1-Phenyl-3-ethyl-5-(γ-anilinoallylidene)-2-thiohydantoin was acetylated with acetic anhydride and triethylamine, and the washed *acetyl* derivative recrystallised from 50% aqueous pyridine (12 c.c. per g.), giving a 67% yield (Found: S, 8·05. $C_{22}H_{21}O_2N_3S$ requires S, 8·2%). The yellow crystals had m. p. 212—214°, whereas in B.P. 470,725 the m. p. is given as 247—249° (decomp.). The absorption maximum was at 4155 A. The substance sensitised a gelatino-chloride plate to 5100 A., with the maximum at 4500 A.

3-*Carboxymethyl*-5-(*γ-anilinoallylidene*)*rhodanine* (IV; R = $CH_2{\cdot}CO_2H$, X = S).—3-Carboxymethylrhodanine (0·96 g.; 2 mols.), β-anilinoacraldehyde anil hydrochloride (1 mol.), absolute alcohol (10 c.c.), and triethylamine (4 mols.) were mixed at room temperature and, after 15 minutes, cooled with ice. The triethylamine salt was filtered off, washed with absolute alcohol (0·67 g. left), and recrystallised from methyl alcohol (5 c.c.). The product (0·60 g.) was taken up in hot methyl alcohol (6 c.c.) and treated with hot acetic acid (6 c.c.), whence a 45% yield of the *acid* was obtained on cooling (Found: S, 20·25. $C_{14}H_{12}O_3N_2S_2$ requires S, 20·05%). The light red crystals had m. p. about 264° (decomp.), with shrinking and darkening from 225°. A methyl-alcoholic solution containing ammonia had its absorption maximum at 4745 A. whilst one containing sulphuric acid had the maximum at 4800 A. The dye sensitised a gelatino-chloride plate from 4500 to 6100 A., the maximum lying at 5500 A., and decreased the blue sensitivity.

2-*Diphenylamino*-4-*keto*-5-(*γ-anilinoallylidene*)-Δ^2-*thiazoline* (V).—2-Diphenylamino-4-keto-Δ^2-thiazoline (0·67 g.; 1 mol.), β-anilinoacraldehyde anil hydrochloride (1 mol.), and triethylamine (2 mols.) in absolute alcohol (5 c.c.) were boiled together for 30 minutes. The washed product (89% yield) was twice recrystallised from methyl alcohol (95 c.c. and 135 c.c. per g.) whereupon the yield was 22% (Found, after drying in a vacuum at 60—80°: S, 8·15. $C_{24}H_{19}ON_3S$ requires S, 8·05%). The orange crystals, with a blue reflex, had m. p. about 257° (decomp.), with darkening from 240°. The absorption maximum of a methyl-alcoholic solution containing ammonia was at 4455 A. and of one containing sulphuric acid at 4680 A. The *thiazoline* sensitised a gelatino-chloride plate to 5500 A., with the maximum at 5000 A.

[4-(1-*Ethyldihydroquinoline*)][5-(3-*ethylrhodanine*)]*dimethin*merocyanine (VIII).—This is mentioned as example 117 of B.P. 450,958. A mixture of 4-β-acetanilidovinylquinoline ethiodide (2·22 g.; 1 mol.), 3-ethylrhodanine (0·81 g.; 1 mol.), absolute alcohol (20 c.c.), and triethylamine (1·0 c.c.; 1·5 mols.) was boiled for 10 minutes. The washed *dye* was recrystallised from pyridine (20 c.c.). The 48% yield was boiled out with methyl alcohol (30 c.c. per g.) and recrystallised from pyridine and water (30 c.c. of each per g.), giving a 43% yield (Found, after drying in a vacuum at 60—80°: S, 18·4. $C_{18}H_{18}ON_2S_2$ requires S, 18·75%). The purple powder had m. p. 226° (decomp.). The principal absorption maximum was at 6140 A., with a secondary one at 5760 A. Sensitisation was from 5600 to 6800 A., with the maximum at 6550 A., and decrease of the blue sensitivity.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro*-*oxazole*)][2-(3-*ethylbenzthiazoline*)]*dimethin*merocyanine (IX; R = Et, X = O).—This is mentioned as example 85 of B.P. 450,958. A mixture of 4-keto-2-thio-3-ethyltetrahydro-oxazole (0·73 g.; 1 mol.), 2-β-acetanilidovinylbenzthiazole ethiodide (1 mol.), triethylamine (2 mols.), and ethyl alcohol (30 c.c.) was boiled for 3 minutes. The washed dye (1·45 g.) was recrystallised from pyridine (15 c.c.) and obtained in 75% yield (Found, after drying in a vacuum at 60—80°: S, 19·5. $C_{16}H_{16}O_2N_2S_2$ requires S, 19·3%). The maroon crystals had m. p. 240° (decomp.), with shrinking from 212°. The absorption maximum was at 5030 A. The *dye* sensitised a gelatino-chloride plate to 5900 A. with the chief maximum at 5500 A., and another at 4750 A. This preparation and the next were carried out by Dr. R. J. Rathbone.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzthiazoline*)]*dimethin*merocyanine (IX; R = Et, X = S).—This *dye* is mentioned as example 88 of B.P. 450,958. Its preparation was like the preceding one but with 3-ethylrhodanine instead of the oxazole derivative. The crude dye (75% yield) was recrystallised from pyridine (40 c.c. per g.), giving a 60% yield (Found: S, 27·8. $C_{16}H_{16}ON_2S_3$ requires S, 27·6%). The bright red crystals had m. p. 265° (decomp.). The absorption maximum was at 5300 A. and the sensitising maximum at 5800 A.

[5-(3-*Carboxymethylrhodanine*)][2-(3-*ethylbenzthiazoline*)]*dimethin*merocyanine (IX; R = $CH_2{\cdot}CO_2H$, X = S).—3-Carboxymethylrhodanine (0·96 g.; 1 mol.), 2-β-acetanilidovinylbenzthiazole ethiodide (1 mol.), triethylamine (1·2 mols.), and ethyl alcohol (8 c.c.) were boiled together for 15 minutes. The crude product (0·75 g.) was recrystallised from pyridine (5 c.c.), then converted into the *acid* by boiling with acetic acid (10 c.c.), resulting in a 25% yield (Found, after drying in a vacuum at 60—80°: S, 25·35. $C_{16}H_{14}O_3N_2S_3$ requires S, 25·45%). The purple powder became scarlet at about 200°, darkened at about

220°, and had m. p. about 273—278° (decomp.). The absorption maximum of a methyl-alcoholic solution containing sulphuric acid was at 5225 A. The dye sensitised to 6400 A., with the maximum at about 5600 A.

[5-(3-*Ethylrhodanine*)][2-(5-*chloro*-3-*ethylbenzthiazoline*)]*dimethin*merocyanine.—5-Acetanilidomethylene-3-ethylrhodanine (1·53 g.; 1 mol.), 5-chloro-2-methylbenzthiazole ethiodide (1 mol.), triethylamine (1·5 mols.), and absolute alcohol (25 c.c.) were boiled together for 3 minutes. The washed product (1·40 g.) was recrystallised from pyridine (80 c.c.) and methyl alcohol (80 c.c.), being obtained in 63% yield (Found, after drying in a vacuum at 60—80°: Cl, 9·3. $C_{16}H_{15}ON_2ClS_3$ requires Cl, 9·3%). The reddish crystals had m. p. 246—248° (decomp.). The absorption maximum was at 5220 A. The *dye* sensitised a gelatino-bromide plate to 6400 A., with maxima at 5800 A. and 5250 A.

[5-(4-*Keto*-2-*thio*-3-*ethyltetrahydro-oxazole*)][2-(3-*ethylthiazolidine*)]*dimethin*merocyanine (X; X = O).—4-Keto-2-thio-3-ethyltetrahydro-oxazole (0·73 g.; 1 mol.), 2-β-acetanilidovinyl-Δ²-thiazoline ethiodide, triethylamine (1·2 mols.), and ethyl alcohol (8 c.c.) were boiled together for 15 minutes. The washed product (1·05 g.) was recrystallised from aqueous pyridine (2 : 1, 21 c.c.) and obtained in 68% yield. After another such recrystallisation, the yield was 41% (Found, after drying in a vacuum at 60—80°: S, 22·3. $C_{12}H_{16}O_2N_2S_2$ requires S, 22·55%). The yellow powder had m. p. 169°. The absorption maximum was at 4575 A. The *cyanine* sensitised a gelatino-chloride plate to 5500 A., the maximum lying at 5000 A.

[2-(3-*Ethylthiazolidine*)][5-(3-*ethylrhodanine*)]*dimethin*merocyanine (X; X = S).—This was prepared by boiling together for 5 minutes, 2-β-anilinovinyl-Δ²-thiazoline ethiodide (3·62 g.; 1 mol.), 3-ethylrhodanine, triethylamine (1·5 mols.), and ethyl alcohol (16 c.c.). The washed product (65% yield) was recrystallised from pyridine and methyl alcohol (8 c.c. of each) and obtained in 23% yield. After a second recrystallisation (5 c.c. pyridine; 15 c.c. MeOH per g.) the yield was 20% (Found, after drying in a vacuum at 60—80°: S, 31·8. $C_{12}H_{16}ON_2S_3$ requires S, 32·05%). The crimson powder had m. p. 161°. The absorption maximum was at 4825 A. The *dye* sensitised to 5800 A. with the maximum at 5350 A.

[2-(3-*Ethylthiazolidine*)][5-(2-*diphenylamino*-4-*keto*-Δ²-*thiazoline*)]*dimethin*merocyanine (XI).—2-Diphenylamino-4-keto-Δ²-thiazoline (2·69 g.; 1 mol.), 2-β-acetanilidovinyl-Δ²-thiazoline ethiodide (1 mol.), triethylamine (1·2 mols.), and ethyl alcohol (15 c.c.) were boiled together for 12 minutes. The washed product (72% yield) was boiled out four times with methyl alcohol (4 × 25 c.c.), and the residue recrystallised from a mixture of acetic acid (15 c.c.) and methyl alcohol (30 c.c.). The substance from the first boiling out was rejected and that from the next three (0·30 g.) added to the main bulk (1·80 g.), making a 52% yield (Found, after drying in a vacuum at 60—80°: S, 15·55. $C_{22}H_{21}ON_3S_2$ requires S, 15·75%). The bright yellow *cyanine* had m. p. 279—281° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 4600 A. A gelatino-chloride plate was sensitised to 5500 A., the maximum lying at 4950 A.

[2-(1-*Ethylquinoline*)][5-(3-*ethylrhodanine*)]*tetramethin*merocyanine (XII).—To 2-(4′-anilino-1′ : 3′-butadienyl)quinoline ethiodide (4·28 g.; 1 mol.) were added acetic anhydride (200 c.c.), triethylamine (2·75 c.c.; 2 mols.), and 3-ethylrhodanine (3·22 g.; 2 mols.), and the mixture was boiled for 4 minutes. The solid was filtered off, washed with acetic anhydride and with ether (2·33 g. left), and boiled out with light petroleum (b. p. 80—100°; 2400 c.c.). The residue (0·76 g.; 38% yield) was recrystallised from benzene (330 c.c. per g.) and gave a 17% yield (Found, S, 17·4. $C_{20}H_{20}ON_2S_2$ requires S, 17·4%). The greyish blue crystals turned green at about 257° and melted about 270° (decomp.). The principal absorption maximum was at 6575 A., with a secondary one at 6150 A. The *cyanine* sensitised from 6200 to 7400 A., with a maximum at 7000 A., but caused some veil.

[5-(1-*Phenyl*-3-*ethyl*-2-*thiohydantoin*)][2-(3-*ethylbenzselenazoline*)]*tetramethin*merocyanine (XIII).—2-(4′-Anilino-1′ : 3′-butadienyl)benzselenazole ethiodide (4·81 g.) was similarly boiled with acetic anhydride, triethylamine, and 1-phenyl-3-ethyl-2-thiohydantoin. The washed product (2·88 g.) was twice boiled out with light petroleum (b. p. 80—100°; 1200 c.c., 2400 c.c.). The substance which separated from the second extract (0·07 g.) was added to the residue (1·69 g.) and boiled out with benzene (120 c.c.), whence a 13% yield crystallised. After recrystallisation from benzene (210 c.c. per g.), the yield of *cyanine* was 5% [Found, micro-analysis by Drs. Weiler and Strauss: N, 8·75. $C_{25}H_{23}ON_3SSe$ requires S, 8·75%). The dull green crystals had m. p. 277° (decomp.). The absorption maximum was at 5590 A. Sensitisation was from 5100 to 7500 A., with the maximum at 6900 A.

The residue (0·44 g.) from the first benzene recrystallisation was again boiled out with benzene (50 c.c.) and this residue (0·35 g.) was recrystallised from methyl alcohol (125 c.c.; 0·16 g. obtained) (Found: I, 21·25. Calc. for $C_{23}H_{23}N_2ISe_2$: I, 20·9%). This by-product had the properties of the known bis-2-(3-ethylbenzselenazole)pentamethincyanine iodide (Fisher and Hamer, *Proc. Roy. Soc.*, 1936, *A*, **154**, 703).

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzthiazoline*)]*tetramethin*merocyanine.—This *dye* was prepared by heating together 2-(4′-anilino-1′ : 3′-butadienyl)benzthiazole ethiodide (4·34 g.), acetic anhydride, triethylamine, and 3-ethylrhodanine. The washed product (2·70 g.) was boiled out with light petroleum (b. p. 80—100°; 2400 c.c.) and the residue (1·30 g.; 35% yield) was thrice recrystallised from benzene (210 c.c. per g.), the yields being 27%, 20%, and 14% (Found: S, 25·95. $C_{18}H_{18}ON_2S_3$ requires S, 25·7%). The greyish-blue crystals had m. p. 238°, with shrinking from 235°. The broad absorption curve had its maximum at 5950 A. Sensitisation was from 6200 to 7300 A., with the maximum at 6900 A., and the original blue sensitivity of the plate was decreased. The preparation of this dye is recorded in B.P. 450,958, example 123.

[5-(1-*Phenyl*-3-*ethyl*-2-*thiohydantoin*)][2-(3-*ethylbenzthiazoline*)]*tetramethin*merocyanine.—This *dye* was prepared from the same anilino-compound (4·34 g.) but with 1-phenyl-3-ethyl-2-thiohydantoin. The washed product (1·89 g.) was boiled out with light petroleum (b. p. 80—100°; 2400 c.c.), and the residue (1·38 g.) boiled out five times with benzene (5 × 20 c.c.). From the first four extracts a 10% yield crystallised. A second recrystallisation from benzene (50 c.c.) gave a 6% yield (Found: S, 14·9. $C_{24}H_{22}ON_2S_3$ requires S, 14·8%). The green crystals decomposed from about 255°. The rounded absorption curve had its maximum at 5650 A. Sensitisation was from 5300 to 7300 A., with fogging and with decrease of the original blue sensitivity.

The dye undissolved at the first benzene extraction was further boiled out with benzene and the

residue (0·57 g.) was recrystallised from methyl alcohol (150 c.c. per g.; 0·32 g. obtained) (Found: I, 24·55. Calc. for $C_{33}H_{33}N_3IS_3$: I, 24·5%).

[2-(3-*Ethyl*-Δ^3-*thiazoline*)][5-(3-*ethylrhodanine*)]*tetramethin*mero*cyanine*.—This was prepared from 2-(4′-anilino-1′ : 3′-butadienyl)-Δ^3-thiazoline ethiodide (1·93 g.), 3-ethylrhodanine, acetic anhydride, and triethylamine, by boiling together for 1 minute. The ether-washed product (1·22 g.) was ground with cold concentrated hydrochloric acid solution (20 c.c.), which dissolved the mero*cyanine*. It was precipitated (30% yield) by adding the extract to hot water (100 c.c.) and treating it with excess of ammonia. After two recrystallisations from benzene (50 c.c. per g.) (yields 19% and 11%) and one from 50% aqueous pyridine (20 c.c. per g.), the final yield was 11% (Found: S, 29·25. $C_{14}H_{18}ON_2S_3$ requires S, 29·5%). The steel-blue crystals had no definite m. p.; softening began at about 175° and violent decomp. occurred at about 280°. The absorption maximum was at 5700 A. Sensitisation was from 5400 to 6900 A., with the maximum at 6300 A.

The product left undissolved by hydrochloric acid was again ground with acid (20 c.c.) and then washed with water. The residue (0·60 g.) was twice recrystallised from pyridine (10 c.c. per g.) and gave a 25% yield of yellow crystals, which by analysis (Found: S, 19·45. Calc. for $C_{16}H_{14}O_2N_2S_2$: S, 19·3%), m. p. and mixed m. p., were identified as 3-ethyl-5-(γ-acetanilidoallylidene)rhodanine (cf. p. 1128).

We thank Mrs. B. Inman for absorption measurements, Dr. B. H. Carroll and Mr. J. Morgan for sensitising tests, and Dr. R. J. Rathbone for two dye preparations. We are particularly indebted to Dr. J. T. Hewitt, F.R.S., and to Dr. A. D. Mitchell for discussing the nomenclature of the *mero*cyanines.

KODAK LTD., WEALDSTONE, HARROW, MIDDLESEX. [*Received, October 21st*, 1948.]

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239. *Replacement of the Diazonium by the Cyano-group in Neutral Solution.*

By HERBERT H. HODGSON and FRED HEYWORTH.

The preparation of cyanides and dicyanides from diazonium and bisdiazonium compounds in neutral solution is described, together with a comparison of the catalytic efficiencies of potassium cupro- and nickelo-cyanides in decompositions of diazonium compounds.

PREVIOUS applications of the Sandmeyer reaction to the preparation of cyanides from diazo-compounds have been limited to monodiazonium salts, mainly in acid solution, although Clarke and Read (*J. Amer. Chem. Soc.*, 1924, **66**, 1001) neutralised their diazonium salt solutions with sodium carbonate before adding them to the cyanide mixture to avoid the subsequent evolution of hydrogen cyanide, and benzene was also added to remove the product from the reaction phase immediately it was formed. Korczynski, Mrczynski, and Vielan (*Rocz. Chem.*, 1921, **1**, 140; cf. also, Korczynski and Fundrich, *Compt. rend.*, 1926, **183**, 421) found that replacement of the copper cyanide as catalyst by nickel cyanide gave somewhat better yields of cyanides, and the improved efficiency was attributed to the greater solubility of the nickel cyanide than of cuprous cyanide in the solution of the excess of potassium cyanide. Other metallic cyanides, such as those of iron, chromium, manganese, zinc, molybdenum, cadmium, and tin, were found to be without catalytic effect. Ashley, Barber, Ewin, Newbery, and Self (*J.*, 1942, 113) and Barber (*J.*, 1943, 79) have investigated the isolation process and the preparation of the cuprous catalyst.

We prepared the cyanides in neutral solution, and compared the relative efficiencies of potassium cupro- and nickelo-cyanides under these conditions. Further, the preparation of dicyanides direct from bisdiazotised homonuclear diamines is described for the first time; although Hodgson and Walker (*J.*, 1935, 530) described the bisdiazotisation of *o*-, *m*-, and *p*-phenylenediamine and their direct conversion into the respective dichlorobenzene, and Schoutissen (*J. Amer. Chem. Soc.*, 1933, **55**, 4531) reported a method for the bisdiazotisation of *m*- and *p*-phenylenediamine and their subsequent direct conversion into dihalogenobenzenes, yet the corresponding dicyanides could not be prepared until Hodgson and Walker (*J.*, 1933, 1620) overcame the difficulty of bisdiazotising the homonuclear diamines, and Hodgson and Mahadevan (*J.*, 1947, 325) isolated the bisdiazonium sulphates in solid form, thereby permitting the use of neutral solutions of these compounds. With nickel cyanide, which was much more efficient than cuprous cyanide, as catalyst, *m*- and *p*-dicyanobenzene were obtained from their respective bisdiazonium salts in 17% and 42% yields, and identified respectively by comparison with an authentic specimen, and by hydrolysis to terephthalic acid. An 8% yield of 2 : 4-dicyanotoluene was obtained from *m*-tolylene-2 ; 4-diamine, but dicyanides could not be obtained from *o*-phenylenediamine and 4-nitro-*o*-phenylenediamine.

Korczynski *et al.* (*loc. cit.*) compared the yields of *p*-bromocyanobenzene and *o*-cyanoanisole from *p*-bromoaniline and *o*-anisidine with cuprous and nickel cyanide, respectively, and this

comparison has now been extended to the diazonium sulphates from twelve amines after neutralisation with calcium carbonate. The comparison confirms their result for *o*-anisidine under the conditions employed, but affords variable data for other amines; for with diazotised aniline and *p*-anisidine, both catalysts are equally effective, but diazotised *o*- and *p*-nitroaniline, *o*- and *p*-chloroaniline, and *o*- and *p*-toluidine give the best yields with the cuprous catalyst, and β-naphthylamine with the nickel salt, but diazotised *m*-nitro- and *m*-chloro-aniline only react with the cuprous catalyst.

Sandmeyer had originally carried out the reaction by the addition of the diazonium solution to the boiling aqueous potassium cuprocyanide, but Clarke and Read (*loc. cit.*) recommended 20—30° as the optimum temperature range; it has now been found that 70—80° is better for most of the decompositions, and, whereas Barber (*loc. cit.*) states that any temperature between 30° and 90° is equally suitable, the yields under the present conditions are favoured by hot decomposition: in contrast to the claim of Clarke and Read, *p*-toluidine gives an improved yield of *p*-cyanotoluene at 70—80°.

Experimental.

Comparison of the Catalytic Efficiencies of Sodium Cupro- and Nickelo-cyanides at 30—40°.—*General procedure.* The amine (2·0 g.) was diazotised in a solution of sulphuric acid (6 c.c., *d* 1·84) and water (10 c.c.) by addition of a solution of sodium nitrite (1·5 g.) in water (7 c.c.), with crushed ice (10—20 g.) to keep the temperature at 0°. Excess acid was removed by addition of the mixture to powdered calcium carbonate (10 g.) and ice (10 g.), and the filtered solution was run into the relevant decomposition mixture (*a*) or (*b*) at 30—40°: (*a*) potassium cuprocyanide was prepared by dissolution of cuprous cyanide (made according to Barber's directions, *J.*, 1943, 79) in potassium cyanide (10 g.) and water (25 c.c.); (*b*) potassium nickelocyanide was prepared by addition of a solution of crystallised nickel sulphate (7 g.) in water (20 c.c.) to one of potassium cyanide (10 g.) in cold water (25 c.c.). After the evolution of nitrogen had ceased, the cyano-compound was removed by steam-distillation, and filtered off from the distillate if solid or ether-extracted if liquid, then weighed and identified. The results are given in the following table.

Amine.	Yield of cyano-compound, %. Catalyst (*a*).	Catalyst (*b*).	Amine.	Yield of cyano-compound, %. Catalyst (*a*).	Catalyst (*b*).
Aniline	17·5	17·5	*p*-Chloroaniline ...	51	32
o-Nitroaniline	65	40	*o*-Anisidine	60	72
m-Nitroaniline ...	28	0	*p*-Anisidine	45	36
p-Nitroaniline ...	67	48	*o*-Toluidine	48	27
o-Chloroaniline ...	67	46	*p*-Toluidine.....	45	36
m-Chloroaniline ...	28	Trace	β-Naphthylamine	14·5	25

Comparison of Decompositions at 20—30° *and at* 70—80°.—*Method.* The sodium cuprocyanide used in these experiments was prepared by dissolving cuprous cyanide (10 g.) in a solution of sodium cyanide (20 g.) in water (50 c.c.), dividing the mixture in two equal parts, and stirring into each half, at the appropriate temperature, a solution of the neutralised diazotised amine (10 g.). The results are compared below:

Amine.	Yield, %, at 70—80°.	Yield, %, at 20—30°.	Amine.	Yield, %, at 70—80°.	Yield, %, at 20—30°.
o-Toluidine	45	18	*o*-Chloroaniline	67	Small
p-Toluidine	48	Small	*m*-Chloroaniline ...	28	21
m-Nitroaniline	23	7	*p*-Chloroaniline	51	14
p-Nitroaniline	21	14			

Simultaneous Replacement of Two Homonuclear Diazonium by Two Cyano-groups.—p-*Phenylenediamine.* The amine (5 g.), dissolved in cold glacial acetic acid (50 c.c.), was added to an ice-cold solution of sodium nitrite (7 g.) in sulphuric acid (40 c.c., *d* 1·84), the mixture being kept until diazotisation was complete, after which dry ether (250 c.c.) was stirred into it, the solid bisdiazonium compound was filtered off, washed with ether (250 c.c.), dissolved in water (30 c.c.) at 0°, and the solution stirred quickly into one of cuprous cyanide (20 g.) and sodium cyanide (30 g.) in water (100 c.c.) at 30°. On steam-distillation, *p*-dicyanobenzene passed over (0·05 g.). On repetition, but with potassium nickelocyanide as catalyst [prepared by adding a solution of crystallised nickel sulphate (20 g.) in water (60 c.c.) to one of potassium cyanide (50 g.) in water (150 c.c.)], *p*-dicyanobenzene (2·5 g., 42·2% yield) passed over on steam-distillation; m. p. 220°, raised to 222° by recrystallisation from acetic acid, and hydrolysed by alcoholic potassium hydroxide followed by acidification to terephthalic acid (2·0 g.) (unmolten at 300°). This acid, on dissolution in methanol with subsequent passage of dry hydrogen chloride, afforded the methyl ester, m. p. 140° (Schwanert, *Annalen*, 1864, **132**, 269, gives m. p. 140°).

m-*Phenylenediamine.* After procedure as above, steam-distillation afforded *m*-dicyanobenzene (1·5 g., 25·4% yield), m. p. 158—160°, which on recrystallisation from ethanol gave colourless crystals, m. p. 159—160° (lit., m. p. 160°).

m-*Tolylene*-2 : 4-*diamine.* This diamine (2 g.), when treated as above, afforded 2 : 4-dicyanotoluene (0·01—0·1 g.) on steam-distillation; it separated from ethanol in colourless crystals, m. p. 142—144° (lit., m. p. 144—145°) (Found: N, 20·0. Calc. for $C_9H_8N_2$: N, 19·7%).

p-*Tolylene*-2 : 5-*diamine.* This base (2 g.) similarly afforded 2 : 5-dicyanotoluene, m. p. 150—152°

(Found: N, 20·0%), which was hydrolysed by boiling aqueous 65% sulphuric acid to toluene-2 : 5-dicarboxylic acid, m. p. 328—330° (lit., m. p. 328—330°).

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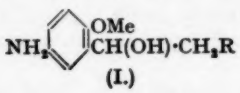
240. *Contributions to the Chemistry of Synthetic Antimalarials. Part VIII. Aromatic Carbinolamines.*

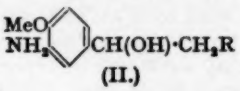
By D. W. MATHIESON and (the late) G. NEWBERY.

The synthesis of some substituted phenylcarbinolamines is described. The products had no significant antimalarial activity.

THE study by King and Work (*J.*, 1940, 1307) of quinoline derivatives bearing carbinolamine side chains suggested an investigation of some benzene derivatives containing similar side chains; various mono- and di-substituted phenylcarbinolamines have been prepared for testing against *Plasmodium gallinaceum*.

Compounds (I; R = morpholino and piperidino), (II; R = morpholino and piperidino), (III; R = NH·CHMe, morpholino, and piperidino), (IV; R = NEt_2, NBu^n_2, morpholino, and


(I.)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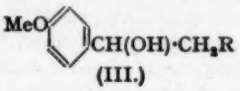
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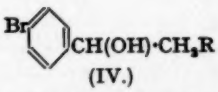
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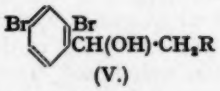

(V.)

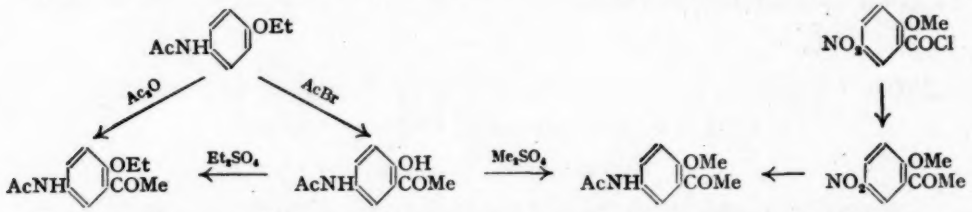
piperidino), and (V; R = morpholino) have been synthesised. Details of the first three examples of series (IV) have already been published by Drake and Goldman (*J. Org. Chem.*, 1946, **11**, 100) whilst Lutz *et al.* (*ibid.*, 1947, **12**, 617) have described the fourth member. Chemical work in these laboratories confirms the results of these authors. None of these compounds except (IV; R = NBu^n_2) and (IV; R = morpholino) showed any activity against *Pl. gallinaceum*.

Nitration of *o*-methoxybenzoic acid (Simonsen and Rau, *J.*, 1917, **111**, 228) gave 5-nitro-2-methoxybenzoic acid which was purified by successive crystallisation from acetic acid and methanol instead of the tedious fractionation of the barium and the calcium salts employed by these authors. Treatment of the corresponding acid chloride with ethereal diazomethane yielded *5-nitro-ω-diazo-2-methoxyacetophenone*. This with hydrogen bromide in chloroform gave an inseparable mixture, one constituent of which, obtained by handpicking, was shown to be the required *ω-bromo-5-nitro-2-methoxyacetophenone* identical with a sample synthesised as described below. The use of hydrogen chloride in ether gave a similar mixture, and the method was not investigated further. It is of interest that *m*-nitro-ω-diazoacetophenone reacts normally with bromine in chloroform to give the ω-bromo-derivative (Evans and Brook, *J. Amer. Chem. Soc.*, 1908, **30**, 406) whereas ω-diazo-*o*-methoxyacetophenone in our hands gave a mixture which could not be satisfactorily purified. 5-Nitro-2-methoxybenzoyl chloride was therefore condensed with ethoxymagnesium-malonic ester by Lund's method (*Ber.*, 1934, **67**, 935), and the resulting *ethyl 5-nitro-2-methoxybenzoylmalonate* hydrolysed to *5-nitro-2-methoxyacetophenone*. Reduction afforded 5-amino-2-methoxyacetophenone from which, by the action of acetic anhydride, *5-acetamido-2-methoxyacetophenone* was obtained. Treatment of *5-nitro-2-methoxyacetophenone* with bromine in chloroform gave ω-bromo-5-nitro-2-methoxyacetophenone.

Nitration of *p*-methoxyacetophenone yielded 3-nitro-4-methoxyacetophenone (Harding, *J.*, 1914, **105**, 2794) which on bromination gave *ω-bromo-3-nitro-4-methoxyacetophenone*.

In early experiments the direct synthesis of the intermediate ω-halogenoacetophenones by the Friedel–Crafts reaction was contemplated, and, in view of the unreactivity of nitro-compounds with aluminium chloride under normal conditions, the substituted acetamido-derivatives were used. *p*-Methoxyacetanilide with acetyl chloride and aluminium chloride gave a complex mixture, partly ketonic in nature, and in view of Kunckell's work (*Ber.*, 1901, **34**, 124; *Ber. deut. pharm. Ges.*, 1913, **23**, 472) attention was turned to *p*-ethoxyacetanilide. This author has described the reaction of acetyl bromide with phenacetin without, however, offering rigorous

proof of the structure of the resulting compound. Repetition of this work yielded a phenolic ketone the methyl ether of which was identical with 5-acetamido-2-methoxyacetophenone. Use of acetic anhydride in place of acetyl bromide gave *5-acetamido-2-ethoxyacetophenone* identical with the product of ethylation of the corresponding 2-hydroxy-compound; thus:



The products, however, were always contaminated by a second substance, ketonic in nature, which was not readily removed and was present in varying proportions in various apparently identical experiments; this method therefore was not further pursued. It is interesting that nitration of phenacetin (Reverdin, *Ber.*, 1876, **29**, 2595; *Rec. Trav. chim.*, 1929, **48**, 838; Hinsberg, *Annalen*, 1896, **292**, 249; Erp, *J. pr. Chem.*, 1931, **129**, 327) yields 2-nitro-4-ethoxyacetanilide, suggesting that the relative orienting power of these two groups is NHAc>OEt. Ingold (*J.*, 1926, 1310) reports that nitration of 2-methoxyacetanilide yields 4-nitro- (74%), 5-nitro- (13%), and 6-nitro-2-methoxyacetanilide (1·5%); again establishing the relative directing powers, in nitration at least, as NHAc>OMe. With the Friedel–Crafts reaction the opposite appears to be the case though, in view of the second fraction reported above, the possibility of the other isomer being present is not excluded. Further work will be reported later.

m-Bromonitrobenzene with iron dust in presence of calcium chloride gave *m*-bromoaniline from which *m*-dibromobenzene was obtained by a Sandmeyer reaction (Holleman, *Rec. Trav. chim.*, 1906, **25**, 186). Contrary to the evidence of Lutz *et al.* (*loc. cit.*) treatment of this with acetyl chloride and aluminium chloride gave 2 : 4-*dibromoacetophenone* in good yield; this constitution being initially assigned by analogy with the work of Montagne and van Charante (*Rec. Trav. chim.*, 1912, **31**, 298) and Böeseken (*ibid.*, 1908, **27**, 15) who similarly synthesised 2 : 4-dichlorobenzophenone. Proof was obtained by oxidation with dilute nitric acid which gave 2 : 4-dibromobenzoic acid, m. p. 167—168° (Cohen and Dutt, *J.*, 1914, **105**, 502, give m. p. 168—169°), from which 2 : 4-dibromobenzamide, m. p. 197°, was obtained (Montagne and van Charante, *Rec. Trav. chim.*, 1912, **31**, 329).

p-Methoxyacetophenone, *p*-bromoacetophenone, and 2 : 4-dibromoacetophenone with bromine in chloroform gave ω-bromo-p-methoxyacetophenone, ω : *p*-dibromoacetophenone and ω : 2 : 4-*tribromoacetophenone*, respectively.

Attempted condensation of ω-bromo-5-nitro-2-methoxyacetophenone and ω-bromo-3-nitro-4-methoxyacetophenone with diethylamine and di-*n*-butylamine yielded uncrystallisable oils which rapidly decomposed in presence of hydrochloric acid. With piperidine and morpholine, however, crystalline *hydrobromides* of 5-nitro-ω-piperidino-2-methoxyacetophenone, 5-nitro-ω-morpholino-2-methoxyacetophenone, 3-nitro-ω-piperidino-4-methoxyacetophenone, and 3-nitro-ω-morpholino-4-methoxyacetophenone were obtained. Treatment of these with hydrogen in the presence of Adams's catalyst led to a smooth uptake in two distinct steps, corresponding to the reduction (*a*) of NO_2 to NH_2 and (*b*) of C:O to CH·OH in this order. 2-*Piperidino*-1-(5′-*amino*-2′-*methoxyphenyl*)*ethanol hydrobromide*, 2-*morpholino*-1-(5′-*amino*-2′-*methoxyphenyl*)*ethanol hydrobromide*, 2-*morpholino*-1-(3′-*amino*-4′-*methoxyphenyl*)*ethanol*, and 2-*piperidino*-1-(3′-*amino*-4′-*methoxyphenyl*)*ethanol* were so obtained.

Reaction of the corresponding ω-bromoacetophenone with the requisite secondary amines, followed by reduction with aluminium *iso*propoxide of the salts of the products yielded 2-diethylamino-1-*p*-bromophenylethanol hydrobromide, 2-di-*n*-butylamino-1-*p*-bromophenylethanol hydrobromide and 2-piperidino-1-*p*-bromophenylethanol hydrochloride, as described by Drake and Goldman (*loc. cit.*). In addition 2-*morpholino*-1-p-*bromophenylethanol hydrobromide*, 2-*morpholino*-1-(2′ : 4′-*dibromophenyl*)*ethanol hydrobromide*, 2-iso*propylamino*-1-p-*methoxyphenylethanol hydrobromide*, 2-*piperidino*-1-p-*methoxyphenylethanol hydrobromide* and 2-*morpholino*-1-p-*methoxyphenylethanol hydrobromide* were similarly obtained.

Experimental.

5-Nitro-2-methoxybenzoyl Chloride.—5-Nitro-2-methoxybenzoic acid (Simonsen and Rau, *J.*, 1917, **111**, 228) (15 g.) and thionyl chloride (25 c.c.) were heated under reflux for 4 hours on the steam-bath.

Excess of thionyl chloride was removed under reduced pressure; the residual solid crystallised from dry benzene in colourless needles (16 g., 95%), m. p. 90—91° (Found: Cl, 16·35. $C_9H_6O_4NCl$ requires Cl, 16·48%).

5-Nitro-ω-diazo-2-methoxyacetophenone.—Treatment of 5-nitro-2-methoxybenzoyl chloride (4·4 g.) in dry benzene (30 c.c.) with excess of ethereal diazomethane yielded, on partial evaporation of the solvent, *5-nitro-ω-diazo-2-methoxyacetophenone* (3·2 g., 72%), m. p. 158—160° (decomp.) (Found: N, 18·8. $C_9H_7O_4N_3$ requires N, 18·9%).

5-Nitro-ω-diazo-2-methoxyacetophenone (3·1 g.) in chloroform (120 c.c.) was treated with 50% aqueous hydrobromic acid, and after 1 hour the aqueous layer was removed and the solvent evaporated from the chloroform layer. Crystallisation of the product from benzene–light petroleum gave a mixture of two crystalline substances which were separated by handpicking; (*A*), m. p. 124—128° (softening at 120°) and (*B*), m. p. 117—118°, which was shown to be *ω-bromo-5-nitro-2-methoxyacetophenone* by mixed m. p. with a synthetic sample described below. In view of the small amount available (*A*) was not further investigated.

Ethyl 5-Nitro-2-methoxybenzoylmalonate.—Magnesium (3·35 g.) was treated with half of a mixture of ethyl malonate (25 g.) and ethanol (19 c.c.) in the presence of carbon tetrachloride (0·5 c.c.). After the initial reaction, moderated by cooling in an ice-bath, had subsided, the second half was added, and when reaction had again ceased, dry ether (100 c.c.) was added and the whole heated under reflux for 1 hour, then filtered. 5-Nitro-2-methoxybenzoyl chloride (25 g.) in dry benzene (40 c.c.) was added and heating under reflux continued for 2 hours. Water (150 c.c.) was next added and the whole shaken vigorously; the benzene layer was separated off, the aqueous layer extracted well with ether, and the combined extracts dried (Na_2SO_4). Evaporation of the solvent gave an oil which rapidly solidified and was crystallised from ethanol. The resultant *ethyl 5-nitro-2-methoxybenzoylmalonate* (37·4 g., 83%) had m. p. 78—79° (Found: C, 53·0; H, 5·3; N, 4·2. $C_{13}H_{17}O_8N$ requires C, 53·1; H, 5·0; N, 4·15%).

5-Nitro-2-methoxyacetophenone.—Hydrolysis of the above ester with boiling 6N-sulphuric acid (400 c.c.) in alcohol (50 c.c.) for 6 hours yielded *5-nitro-2-methoxyacetophenone* (60%), m. p. 98° (Found: N, 7·2; OMe, 15·9. $C_9H_9O_4N$ requires N, 7·2; OMe, 15·9%). The *semicarbazone* crystallised in colourless needles, m. p. 215—216°, from alcohol (Found: N, 22·0. $C_{10}H_{12}O_4N_4$ requires N, 22·1%). The 2 : 4-*dinitrophenylhydrazone*, m. p. 239°, separated in orange clusters from acetic acid (Found: N, 18·6. $C_{15}H_{13}O_7N_5$ requires N, 18·65%).

5-Amino-2-methoxyacetophenone.—5-Nitro-2-methoxyacetophenone (4 g.), ethanol (50 c.c.), and granulated tin (4 g.) were treated with hydrochloric acid (*d* 1·18; 18 c.c.) added portionwise at 25°. The nitro-compound and the tin gradually dissolved during 4 hours. After being left for 12 hours the liquid was concentrated to half bulk. The stannichloride which separated was dissolved in water (100 c.c.), and the solution basified with 25% sodium hydroxide (phenolphthalein) and then extracted with ether. Evaporation of the dried (Na_2SO_4) extract gave 5-amino-2-methoxyacetophenone (2·14 g., 65%), b. p. 125—127°/0·25 mm., characterised as the *hydrochloride*, m. p. 186° (decomp.) (Found: N, 7·0; Cl, 17·8. $C_9H_{11}O_2N$,HCl requires N, 6·95; Cl, 17·6%). The N-*acetyl* derivative crystallised from ethanol in needles, m. p. 186—187° (Found: C, 63·9; H, 6·5; N, 6·8; OMe, 15·3. $C_{11}H_{13}O_3N$ requires C, 63·7; H, 6·3; N, 6·8; OMe, 15·0%). *5-Acetamido-2-methoxyacetophenone* 2 : 4-*dinitrophenylhydrazone*, m. p. 205—206°, crystallised in fine rosettes of scarlet needles from acetic acid (Found: N, 15·7. $C_{17}H_{17}O_8N_5,C_2H_4O_2$ requires N, 15·7%). Similarly the *semicarbazone*, m. p. 216—217°, formed cream micro-needles from ethanol (Found: N, 21·2. $C_{12}H_{16}O_3N_4$ requires N, 21·2%).

ω-Bromo-5-nitro-2-methoxyacetophenone.—5-Nitro-2-methoxyacetophenone (2·5 g.) in chloroform (35 c.c.) was treated with bromine (2 g.) in sunlight. After 30 minutes the solution became colourless and hydrogen bromide was evolved. Evaporation gave *ω-bromo-5-nitro-2-methoxyacetophenone*, which crystallised from benzene in colourless needles (1·15 g.), m. p. 119° (Found: N, 5·25; Br, 29·0. $C_9H_8O_4NBr$ requires N, 5·15; Br, 29·2%). The *benzoate*, m. p. 142°, crystallised in colourless plates from ethanol (Found: N, 4·5. $C_{16}H_{13}O_5N$ requires N, 4·45%).

ω-Bromo-3-nitro-4-methoxyacetophenone.—3-Nitro-4-methoxyacetophenone (3 g.) (cf. Harding, *J.*, 1914, **105**, 2794) in dry chloroform (35 c.c.) was treated, as described above, with dry bromine (2·1 g.) in chloroform (8 c.c.). The *product* (2·5 g.) crystallised from ethanol in pale buff needles, m. p. 96° (Found: N, 5·3; Br, 29·2. $C_9H_8O_4NBr$ requires N, 5·15; Br, 29·2%).

Acylation of Phenacetin.—(*a*) *With acetyl bromide* (cf. Kunckell, *Ber. deut. pharm. Ges.*, 1913, **23**, 472). Phenacetin (20 g.) and acetyl bromide (40 g.) in carbon disulphide (60 c.c.) were stirred with anhydrous aluminium chloride (60 g.). After the mixture had been heated under reflux for 1 hour on the steam-bath the solvent was distilled off and the residue treated with ice, giving 5-acetamido-2-hydroxyacetophenone (16 g., 65%) as yellow cubes, m. p. 165°, from ethanol. The 2 : 4-*dinitrophenylhydrazone*, m. p. 290° (decomp.), crystallised in orange needles from acetic acid (Found: N, 18·6. $C_{15}H_{15}O_8N_5$ requires N, 18·75%). 5-Acetamido-2-hydroxyacetophenone (1·8 g.) in water (10 c.c.) containing sodium hydroxide (0·4 g.) was shaken with ethyl sulphate (1 g.) for 2 hours. The precipitate, on recrystallisation from ethanol, gave 5-acetamido-2-ethoxyacetophenone (1·4 g.) m. p. 155—156°. Methylation with methyl toluene-*p*-sulphonate similarly gave 5-acetamido-2-methoxyacetophenone, m. p. 186—188°. The 2 : 4-dinitrophenylhydrazone had m. p. 205°. Neither gave any depression in m. p. on admixture with the synthetic samples described above.

(*b*) *With acetic anhydride.* Phenacetin (20 g.) and acetic anhydride (12 g.) in carbon disulphide (150 c.c.) were stirred with anhydrous aluminium chloride (30 g.). After being left overnight at room temperature the solution was concentrated by removal of the solvent and the residue decomposed with ice-water. After four recrystallisations from ethanol and two from benzene, 5-acetamido-2-ethoxyacetophenone (3 g.) was obtained, m. p. 155° (Kunckell, *loc. cit.*, gives m. p. 155°), identical with the sample above (Found: C, 65·3; H, 6·6; N, 6·45; OEt, 20·5. Calc. for $C_{12}H_{15}O_3N$: C, 65·2; H, 6·75; N, 6·35; OEt, 20·4%). The 2 : 4-*dinitrophenylhydrazone*, m. p. 232—233° (decomp.), separated in golden-orange needles from acetic acid (Found: N, 15·25. $C_{18}H_{19}O_8N_5,C_2H_4O_2$ requires N, 15·2%). The *semicarbazone*, m. p. 238—239°, formed colourless needles from ethanol (Found: C, 55·8; H, 6·5; N, 19·9. $C_{13}H_{18}O_3N_4$ requires C, 56·1; H, 6·5; N, 20·0%).

Fractionation of the residue left after evaporation of the mother liquors from the above recrystallisations gave an unidentified product (0·25 g.), m. p. 111—112°.

ω-Bromo-p-methoxyacetophenone and ω-p-dibromoacetophenone.—These were prepared by bromination of *p*-methoxy- and *p*-bromo-acetophenone (*Org. Synth.*, Coll. Vol. I, p. 109).

2 : 4-*Dibromoacetophenone.*—*m*-Bromonitrobenzene (*Org. Synth.*, Coll. Vol. I, p. 123) (10 g.) in ethanol (30 c.c.) was boiled with calcium chloride (0·6 g.) in water (12 c.c.). After removal from the steam-bath, reduced iron (10 g.) was added slowly in 1 g. portions at such a rate that the heat of reaction kept the solution boiling gently under reflux. The mixture was then heated under reflux for 30 minutes and filtered, and the alcohol distilled off. After addition of hydrochloric acid (*d* 1·16, 20 c.c.) the non-basic substances were extracted with ether. The aqueous layer yielded *m*-bromoaniline, b. p. 122—124°/10 mm. (Holleman, *Rec. Trav. chim.*, 1906, **25**, 186, cites b. p. 130°/12 mm.) (6·4 g., 80%; on the scale of 120 g. of *m*-bromonitrobenzene however the yield fell to 68%).

m-Bromoaniline (68 g.) in sulphuric acid (*d* 1·84, 44 c.c.) and water (2 l.) was diazotised at 5° with sodium nitrite (27 g.) in water (50 c.c.). Cuprous bromide (*Org. Synth.*, Coll. Vol. I, p. 136) was then added at 75° with vigorous stirring. Steam distillation of the mixture followed by ether extraction of the distillate gave *m*-dibromobenzene (23 g.), a colourless oil, b. p. 94°/15 mm., characterised as 2 : 4-dibromobenzenesulphonyl chloride, m. p. 81—82°, and as 2 : 4-dibromobenzenesulphonamide, m. p. 191—192° (Huntress and Carten, *J. Amer. Chem. Soc.*, 1940, **62**, 511, give m. p. 78—79° and m. p. 188—189°, respectively, for these two compounds). *m*-Dibromobenzene (46 g.) and acetyl chloride (33 g.) in dry carbon disulphide (500 c.c.) were heated under reflux with anhydrous aluminium chloride (140 g.) for 6 hours. After decomposition of the product with ice-water and extraction with benzene, 2 : 4-*dibromoacetophenone* (38·25 g., 71%) was obtained, which crystallised from light petroleum (b. p. 60—80°), m. p. 61—62° (Found : C, 34·9; H, 2·5; Br, 57·1. $C_8H_6OBr_2$ requires C, 34·6; H, 2·2; Br, 57·5%). The 2 : 4-*dinitrophenylhydrazone* had m. p. 175° (Found : N, 12·4; Br, 35·4. $C_{14}H_{10}O_4N_4Br_2$ requires N, 12·2; Br, 35·0%).

2 : 4 : *ω-Tribromoacetophenone.*—2 : 4-Dibromoacetophenone (36 g.) in dry chloroform (200 c.c.) was treated with bromine (20·6 g.). The yellow *product* (43 g., 93%) had m. p. 34—35° and b. p. 193—195°/10 mm. (Found : Br, 66·7. $C_8H_5OBr_3$ requires Br, 67·2%).

ω-Dialkylaminoacetophenones.—*General procedure.* The ω-bromoacetophenone (1 mol.) in dry ether was treated with the requisite amine (2 mols.) and left for 2—24 hours by which time 1 mol. of amine hydrobromide had been precipitated. This was filtered off and the filtrate treated with hydrogen chloride or bromide to precipitate the ω-amino-ketone salt which was then recrystallised from ethanol–ether. Excess of hydrogen halide was avoided as this tended to precipitate the products as gums which slowly decomposed. If an oil was formed trituration with dry ether reversed the change where this had not proceeded too far. The compounds listed in the table were so obtained.

				Analysis.			
				Found, %.		Required, %.	
Acetophenone.	No.	Formula of salt.	M. p.	N.	Br.	N.	Br.
5-Nitro-ω-piperidino-2-methoxy-	1	$C_{14}H_{18}O_4N_2$,HBr	195—196° (decomp.)	7·8	22·2	7·8	22·25
5-Nitro-ω-morpholino-2-methoxy-	2	$C_{13}H_{16}O_5N_2$,HBr	197—198 (decomp.)	7·8	22·4	7·76	22·2
3-Nitro-ω-piperidino-4-methoxy-	3	$C_{14}H_{18}O_4N_2$,HBr	186—187 (decomp.)	7·75	22·3	7·8	22·25
3-Nitro-ω-morpholino-4-methoxy-	4	$C_{13}H_{16}O_5N_2$,HBr	210 (decomp.)	7·6	21·9	7·76	22·2
p-Bromo-ω-diethylamino-	5	$C_{12}H_{16}ONBr$,HCl	170—171	—	—	—	—
p-Bromo-ω-di-*n*-butylamino-	6	$C_{16}H_{24}ONBr$,HBr	176—177	—	—	—	—
p-Bromo-ω-piperidino-.....	7	$C_{13}H_{16}ONBr$,HCl	224—225	—	—	—	—
p-Bromo-ω-morpholino-	8	$C_{12}H_{14}O_2NBr$,HBr	248—249	4·0	43·75	3·8	43·8
p-Bromo-ω-*iso*propylamino-	9	$C_{11}H_{14}ONBr$,HBr	246—248	4·2	47·5	4·15	47·5
2 : 4-Dibromo-ω-morpholino-	10	$C_{12}H_{13}O_2NBr$,HBr	223	3·2	54·0	3·2	54·0
ω-Diethylamino-*p*-methoxy-	11	$C_{13}H_{19}O_2N$,HBr	111—112	4·6	(C, 52·0) (H, 6·8)	4·6	(C, 5·7) (H, 6·6)
ω-Piperidino-*p*-methoxy-.....	12	$C_{14}H_{19}O_2N$,HBr	188—189	4·4	25·3	4·5	25·4
ω-*iso*Propylamino-*p*-methoxy- ...	13	$C_{12}H_{17}O_2N$,HBr	171—172	4·9	27·9	4·9	27·8
ω-Morpholino-*p*-methoxy-	14	$C_{13}H_{17}O_3N$,HBr	210	4·36	25·4	4·43	25·3

Reduction of compounds 5, 6, 7, 8, and 10 was carried out with aluminium *iso*propoxide as described by Drake and Goldman (*loc. cit.*) except that the salts were reduced directly instead of as the free base. There were thus obtained 2-diethylamino-1-*p*-bromophenylethanol hydrobromide (64%), m. p. 135—136° (Found : C, 40·5; H, 5·5; N, 4·0; active H, 2. Calc. for $C_{12}H_{18}ONBr$,HBr : C, 40·8; H, 5·4; N, 4·0%; active H, 2); 2-di-*n*-butylamino-1-*p*-bromophenylethanol hydrobromide (68%), m. p. 110—112° (lit. 112—113°) (Found : C, 46·9; H, 6·5; N, 3·6; active H, 2. Calc. for $C_{16}H_{26}ONBr$,HBr : C, 46·9; H, 6·6; N, 3·4%; active H, 2); 2-piperidino-1-*p*-bromophenylethanol hydrochloride (89%), m. p. 236° (lit. 237—238°) (Found : C, 48·6; H, 5·7; N, 4·4; active H, 2. Calc. for $C_{13}H_{18}ONBr$,HCl : C, 48·7; H, 5·9; N, 4·4%; active H, 2); 2-*morpholino*-1-p-*bromophenylethanol hydrobromide* (75%), m. p. 232° (Found : C, 39·0; H, 4·6; active H, 1·8. $C_{12}H_{16}O_2NBr$,HBr requires C, 39·2; H, 4·6%; active H, 2); 2-*morpholino*-1-(2′ : 4′-*dibromophenyl*)*ethanol hydrobromide* (56%), m. p. 215—218° (Found : C, 32·6; H, 3·6; active H, 2. $C_{12}H_{15}O_2NBr_2$,HBr requires C, 32·3; H, 3·6%; active H, 2). Compound 9 could not be reduced to a pure alcohol either by the use of aluminium *iso*propoxide or by hydrogenation under the conditions described below.

In the series of *p*-methoxy-compounds reduction was effected by hydrogenating the amino-ketone in

alcohol at normal temperature and pressure in the presence of (10%) Adams's catalyst. From compounds 12, 13, and 14 were obtained 2-*piperidino*-1-p-*methoxyphenylethanol hydrobromide* (75%), m. p. 164—165° (Found : C, 53·2; H, 6·8; N, 4·5; Br, 25·3; OMe, 9·8. $C_{14}H_{21}O_2N$,HBr requires C, 53·2; H, 7·0; N, 4·4; Br, 25·3; OMe, 9·8%); 2-iso*propylamino*-1-p-*methoxyphenylethanol hydrobromide*, m. p. 110—111° (Found : C, 49·4; H, 6·8; OMe, 10·7; active H, 2·6. $C_{12}H_{19}O_2N$,HBr requires C, 49·65; H, 6·9; OMe, 10·7%; active H, 3); and 2-*morpholino*-1-p-*methoxyphenylethanol hydrobromide* (75%), m. p. 170—171° (Found : C, 49·2; H, 6·3; active H, 2. $C_{13}H_{19}O_3N$,HBr requires C, 49·0; H, 6·3%; active H, 2).

Compounds 1, 2, 3, and 4 were similarly reduced, and gave, respectively, 2-*piperidino*-1-(5′-*amino*-2′-*methoxyphenyl*)*ethanol hydrobromide*, m. p. 151—152° (Found : C, 50·4; H, 7·3; N, 8·3; OMe, 9·4; active H, 3·04. $C_{14}H_{22}O_2N_2$,HBr requires C, 50·7; H, 7·0; N, 8·3; OMe, 9·4%; active H, 3) [the free *base* had m. p. 115° and b. p. 155° (bath temp.)/0·05 mm. (Found: C, 67·7; H, 8·5; active H, 2. $C_{14}H_{22}O_2N_2$ requires C, 67·2; H, 8·8%; active H, 2)]; 2-*morpholino*-1-(5′-*amino*-2′-*methoxyphenyl*)*ethanol hydrobromide*, m. p. 184—185° (Found : C, 46·2; H, 6·0; active H, 2·2. $C_{13}H_{20}O_3N_2$,HBr requires C, 46·9; H, 6·3%; active H, 2); 2-*piperidino*-1-(3′-*amino*-4′-*methoxyphenyl*)*ethanol*, b. p. 175—185°(bath temp.)/0·1 mm. (Found : C, 67·2; H, 8·8; N, 11·2; OMe, 12·3; active H, 1·7. $C_{14}H_{22}O_2N_2$ requires C, 67·2; H, 8·8; N, 11·2; OMe, 12·4%; active H, 2); and 2-*morpholino*-1-(3′-*amino*-4′-*methoxyphenyl*)-*ethanol*, m. p. 66—67°, b. p. 85—90°/10^{-4} mm. (Found : C, 61·95; H, 7·4; active H, 1·75. $C_{13}H_{20}O_3N_2$ requires C, 61·9; H, 7·9%; active H, 2).

The authors thank Mr. S. Bance, B.Sc., A.R.I.C., for the semi-micro-analyses, Mr. G. J. Hill for help with the experimental work, and the Directors of May and Baker Ltd. for permission to publish these results.

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DAGENHAM.

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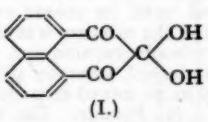
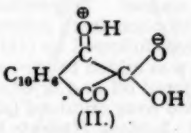
241. peri*Naphthindane*-1 : 2 : 3-*trione, and a Note on the Colour Reaction between its Hydrate and α-Amino-acids.*

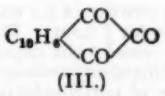
By RADWAN MOUBASHER and (in part) WILLIAM IBRAHIM AWAD.

*peri*Naphthindane-1 : 2 : 3-trione has been prepared by the action of thionyl chloride on its hydrate, or by pyrolysis of the latter. An inner-salt formula (II) for the hydrate is advanced, and some new reactions are described. The nature of the colour reaction between α-amino-acids and the hydrate is discussed.

ERRERA (*Gazzetta*, 1913, **43**, I, 585; **44**, II, 18) heated *peri*naphthindane-1 : 2 : 3-trione hydrate (I) and obtained a red substance, believed to be the anhydrous compound (III), but he did not give an analysis. The latter can be prepared by heating (I) with thionyl chloride, or by heating it in a vacuum. The trione forms orange-red needles, which melt to a dark red liquid; on cooling, the red crystals are re-formed. When the red solution of the triketone in benzene is shaken with water, it is gradually decolorised owing to formation of the hydrate (I). The hydrate is

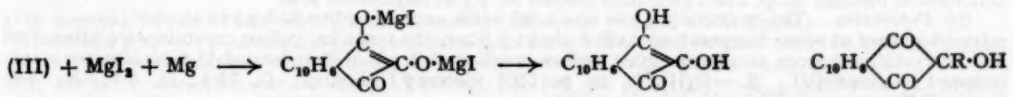

(I.)


(II.)


(III.)

readily soluble in cold water, and in order to explain this solubility and the remarkable thermal stability of (I), the inner-salt structure (II) is assigned to it. The possibility of resonance between (I) and (II) should be stressed (compare the inner-salt formula of ninhydrin, Schönberg and Moubasher, *J.*, 1943, 71).

Gomberg and Bachmann's reagent (*J. Amer. Chem. Soc.*, 1927, **49**, 2584) reduces *peri*naphthindane-1 : 2 : 3-trione to the dihydroxy*peri*naphthindenone (V), and the following mechanism is advanced :


(IV.) (V.) (VI.)

The hydrate (I) reacts with pyrrole, piperidine, and *p*-aminobenzoic acid giving the 2-*substituted* 2-*hydroxy*-peri*naphthindane*-1 : 3-*diones* of type (VI). This reaction is similar to that of bases, *e.g.*, aniline, and allied substances on (I) (Moubasher and Mostafa, *J.*, 1947, 130).

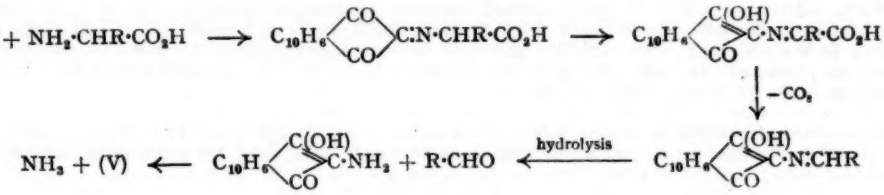
Further study of the reaction of the hydrate (I) with α-amino-acids has led to interesting

results, for a deep pink colour is produced on warming a mixture of the two in aqueous solution. The reaction has been applied to many α-amino-acids, but appears to fail with β-amino-acids.

It gives, moreover, an intensely pink colour with blood albumin, egg albumin, and casein in alcoholic solutions, and a strong orange coloration is produced by normal human urine.

A pink colour is also obtained in presence of ammonia. This colour becomes violet and finally reddish-violet as the concentration of ammonia increases.

The reaction between ninhydrin and α-amino-acids has been discussed by Moubasher and Ibrahim (this vol., p. 702), and the reaction with the analogous *peri*naphthindane-1 : 2 : 3-trione hydrate follows a similar course, affording the compound (V) *via* several coloured intermediate stages :



Experimental.

Preparation of peri*Naphthindane*-1 : 2 : 3-*trione*.—(1) *By the action of thionyl chloride on its hydrate.* Freshly distilled thionyl chloride (50 c.c.) was heated on a steam-bath for about 40 minutes with the hydrate (0·5 g.) recently crystallised from water. The reaction vessel was connected by means of a ground-glass joint to a condenser fitted with a receiver connected to a filter pump, and the apparatus exhausted. The substance dissolved, forming an intensely red solution; as this became more concentrated (owing to evaporation of thionyl chloride), reddish crystals of *peri*naphthindane-1 : 2 : 3-trione separated. After about 50 minutes, the thionyl chloride had distilled off, and the vessel was placed in a vacuum desiccator containing sodium hydroxide in order to remove the last traces. The *trione* (yield, quantitative) melted at 265° (brown-red melt) (Found : C, 74·6; H, 3·2. $C_{13}H_6O_3$ requires C, 74·3; H, 2·8%).

(2) *By thermal decomposition.* The hydrate (0·5 g.) was heated in a vacuum at 250° (bath temp.) for ½ hour; it turned red and a sublimate of red needles was formed (m. p. 265°, brown-red melt), identical with those obtained in (1).

Properties of peri*Naphthindane*-1 : 2 : 3-*trione*.—It sublimes in a vacuum forming intensely red crystals. It dissolves in benzene, phenyl cyanide, xylene, or nitrobenzene at 100°, red solutions being formed. It is practically insoluble in light petroleum (b. p. 50—60°). It dissolves in concentrated sulphuric acid, giving an intensely violet coloration which changes to orange after some time. It gives with sodium hydroxide an intensely blue coloration.

Action of water. The trione was heated for about 5 minutes with a small quantity of water in absence of sunlight. When the hot solution was filtered, concentrated somewhat, and allowed to cool, yellowish crystals of the hydrate were obtained (yield, quantitative), m. p. 273° undepressed with an authentic specimen. When the trione was left at room temperature in May, it changed to the hydrate during 3 hours.

Action of Gomberg and Bachmann's reagent. To powdered magnesium (4 g.) in a mixture of dry ether (50 c.c.) and dry benzene (50 c.c., thiophen-free) iodine was added until its colour persisted. Dry magnesium powder (4 g.) was then added, followed by (III) (0·7 g.), and the mixture was shaken at room temperature for ½ hour. The product was added to ice-cold dilute hydrochloric acid and left overnight in an open vessel; the deposit was filtered off and crystallised from alcohol, whereby silky red needles (0·5 g.) of dihydroxy*peri*naphthindenone were obtained (identified by m. p., mixed m. p., and properties).

Reaction of peri*Naphthindane*-1 : 2 : 3-*trione Hydrate with Bases.*—(a) *Pyrrole.* The hydrate (1 g.), dissolved in water (50 c.c.), and pyrrole (1 g.), in 20 c.c. of alcohol, were mixed at room temperature and set aside; in 10 minutes the clear solution became turbid and a crystalline solid was deposited, and after an hour this was filtered off and recrystallised from alcohol, forming yellow needles of 2-*hydroxy*-2-1′-*pyrryl*peri*naphthindane*-1 : 3-*dione* (VI; R = C_4H_4N) (Found : C, 73·9; H, 4·2; H, 5·2. $C_{17}H_{11}O_3N$ requires C, 73·6; H, 3·9; N, 5·0%). It starts to decompose at 180° and melts at 200° (brown melt). It is soluble in alcohol or benzene, and gives a brown colour with concentrated sulphuric acid.

When this substance was heated under reflux with 10% sodium hydroxide solution (50 c.c.), a green coloration was first formed, changing to an intensely green-blue on cooling. The mixture was then acidified and cooled, whereby a crystalline colourless substance was produced; recrystallised from alcohol, this formed needles, m. p. 273°, identified (mixed m. p.) as naphthalic acid.

(b) *Piperidine.* The hydrate (1 g.) in 50 c.c. of water and piperidine (0·5 g.) in alcohol (10 c.c.) were mixed together at room temperature; after about ½ hour, the resulting yellow crystals were filtered off and recrystallised from alcohol, forming yellow needles (1·2 g.) of 2-*hydroxy*-2-1′-*piperidino*peri*naphindane*-1 : 3-*dione* (VI; R = $C_5H_{10}N$), m. p. 150° (decomp.) (Found : C, 73·1; H, 5·7; N, 4·9. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·7; N, 4·9%).

(c) p-*Aminobenzoic acid.* The hydrate (1 g.) in water (25 c.c.) and *p*-aminobenzoic acid (0·7 g.) in acetic acid (25 c.c.) were heated together on a steam-bath for 20 minutes; the resulting deep green crystals were filtered off and recrystallised from alcohol; 2-*hydroxy*-2-p-*carboxyanilino*peri*naphthindane*-1 : 3-*dione* (VI; R = NH·C_6H_4·CO_2H) formed yellowish-green needles (0·9 g.) decomposing at 185° and melting at 350° (Found : N, 3·9. $C_{22}H_{13}O_5N$ requires N, 4·0%).

Action of peri*Naphthindane*-1 : 2 : 3-*trione Hydrate on α-Amino-acids.*—On mixing a slightly warmed

aqueous solution of the hydrate and glycine, an intensely pink colour is developed immediately, and the intensely red dihydroxy*peri*naphthindenone (V) is soon precipitated. All the other α-amino-acids tested react almost as rapidly as does glycine, and only mere traces are required : the hydrate in 10,000 parts of water gives the characteristic pink colour with α-amino-acids in 15,000 parts of water.

The shade of pink coloration produced shows but slight variations with the various α-amino-acids tested, *viz.*, glycine, DL-alanine, leucine (synthetic), DL-*iso*leucine, DL-norleucine, cysteine hydrochloride, aspartic acid, D-glutamic acid, phenylaminoacetic acid, phenylalanine, (−)-tyrosine, and DL-tryptophan.

This reaction is now being investigated with a view to the determination of α-amino-acids with the aid of a spectrophotometer.

Of the β-amino-acids, only β-aminopropionic and β-aminophenylpropionic acids have been tested, but they do not give any colour under the above conditions.

In the same dilution as above the hot reagent yields with dilute ammonia a strong pink coloration, but it is violet or reddish-violet with more concentrated solutions.

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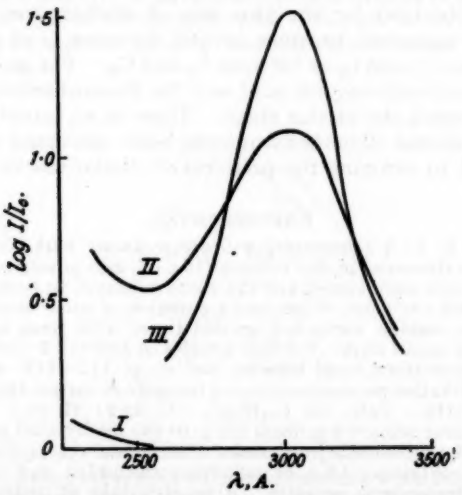
242. *The Reaction of Methyl Tetramethyl Glucosaccharate with Sodium.*

By L. F. WIGGINS.

When methyl tetramethyl glucosaccharate is treated with sodium in toluene in the presence of a trace of methyl alcohol an unexpected reaction occurs. The product isolated is methyl 2 : 5-dimethoxymuconate, probably the *cis–trans* isomer. The relation of this phenomenon to that occurring when mannosaccharodilactone is treated with diazomethane (Schmidt and Kraft, *Ber.*, 1941, **74**, 33) is discussed.

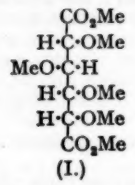
TREATMENT of methyl 2 : 3 : 4 : 5-tetramethyl D-glucosaccharate (I) with sodium in boiling toluene containing a trace of methyl alcohol afforded an unsaturated crystalline compound, m. p. 118°. Analytical results showed that it had been formed from (I) by elimination of two molecules of methanol and that it had the formula $C_{10}H_{14}O_6$. Four methyl groups were present in the compound, and, of these, two were present as carbomethoxy-residues. The unsaturation of the compound was such as to give rise to a system which showed strong selective absorption of ultra-violet light. The same characteristic absorption band makes its appearance when methyl tetramethyl glucosaccharate is boiled for a few minutes in ethyl-alcoholic solution



I. *Methyl* 2 : 3 : 4 : 5-*tetramethyl glucosaccharate* (*c*, 126·4 *mg. per* 100 *ml. in* EtOH).
II. *Methyl* 2 : 3 : 4 : 5-*tetramethyl glucosaccharate after being boiled for* 5 *minutes with* 1 *drop of* 5N-NaOH, *cooled, and diluted to* ca. 12·6 *mg. per* 100 *ml. in* EtOH. $\lambda_{max.}$ 3030 A., ε ca. 2500.
III. *Methyl* 2 : 5-*dimethoxymuconate* (*c*, 1·25 *mg. per* 100 *ml. in* EtOH). $\lambda_{max.}$ 3030 A., ε ca. 27,600. $\lambda_{max.}$ 3038 A., ε ca. 27,600.

containing a drop of 5N-sodium hydroxide (see Fig.). The compound was evidently identical with methyl dimethoxymuconate (II) previously obtained by Haworth, Hirst, and Jones (*J.*, 1938, 710) and by Schmidt and Kraft (*Ber.*, 1941, **74**, 33). Confirmation of this structure (II) assigned to the unsaturated compound was forthcoming from the observation that it underwent

smooth catalytic hydrogenation with the consumption of four atomic proportions of hydrogen and formation of methyl *meso*-2 : 5-dimethoxyadipate (III) (Schmidt and Kraft, *loc. cit.*).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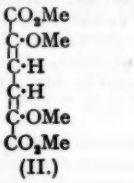
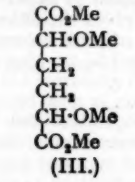
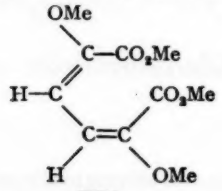

(II.)


(III.)

Methyl 2 : 5-dimethoxymuconate may exist in three forms, the *cis-cis* (IV), the *trans-trans* (V), and the *cis-trans* (VI), and the question arises as to which of these three is the product of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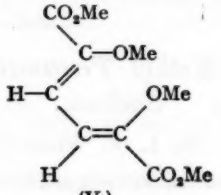
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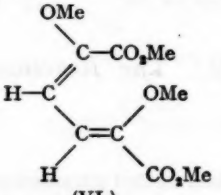
(VI.)

m. p. 118° obtained by the action of sodium on methyl 2 : 3 : 4 : 5-tetramethyl D-glucosaccharate. When the elements of methyl alcohol are removed from C_2 and C_3 and C_4 and C_5 of the model of this compound, methyl *cis-trans*-2 : 5-dimethoxymuconate results. It would appear, therefore, that the methyl 2 : 5-dimethoxymuconate, m. p. 118°, is the *cis-trans*-isomer.

On the other hand, when the elements of methyl alcohol are removed from C_2 and C_3, and C_4 and C_5 of the model of methyl 2 : 3 : 4 : 5-tetramethyl D-mannosaccharate to form methyl 2 : 5-dimethoxymuconate, the *trans-trans*-form is obtained. It is noteworthy that when Schmidt and Kraft (*Ber.*, 1941, **74**, 33) and Haworth, Heslop, Salt, and Smith (*J.*, 1944, 217) subjected mannosaccharodilactone to methylation with methyl iodide and silver oxide or to the action of diazomethane, they obtained, among other products, methyl 2 : 5-dimethoxymuconate, m. p. 140°, and in no case was the isomer, m. p. 118°, isolated. Thus, it is suggested that the substance, m. p. 140°, obtained by the two sets of workers mentioned previously is the *trans-trans*-isomer. This argument becomes invalid, however, if at any time a double bond is transitorily formed between C_1 and C_2 or between C_5 and C_6. The possible relationship between the different forms of dimethoxymuconic acid and the stereochemistry of their saccharic acid precursors are merely pointed out at this stage. There is no intention to state dogmatically the structures of the particular dimethoxymuconic acids discussed above. In view of these conclusions it is intended to examine the products of similar reactions with saccharic acids of different configurations.

Experimental.

Treatment of Methyl 2 : 3 : 4 : 5-Tetramethyl D-Glucosaccharate with Sodium.—Methyl tetramethyl D-glucosaccharate (2 g.) was dissolved in dry toluene (15 c.c.), and powdered sodium (0·5 g.) added. A few drops of dry methyl alcohol were added, and the mixture heated to boiling and continuously shaken for 1 hour. There was a brisk evolution of gas and separation of some tarry matter. The clear upper layer was decanted and the residue extracted several times with fresh toluene. The extracts were combined and evaporated to small bulk; the fine needles of methyl 2 : 5-dimethoxymuconate (0·3 g.) which separated, when recrystallised from toluene, had m. p. 117—118° and were optically inactive. The substance decolourised alkaline permanganate and bromine in carbon tetrachloride (Found : C, 52·5; H, 5·9; OMe, 53·9; equiv., 119. Calc. for $C_{10}H_{14}O_6$: C, 52·2; H, 6·1; OMe, 53·9%; equiv., 115). The yield was variable, the best being 0·4 g. from 1·1 g. of the methylated glucosaccharic acid ester.

Hydrogenation of Methyl 2 : 5-Dimethoxymuconate.—The crystals (0·4 g.) were dissolved in dry methyl alcohol, palladised charcoal containing 0·1 g. of palladium was added, and the mixture was shaken with hydrogen at slightly over atmospheric pressure. A rapid uptake of hydrogen occurred, and reaction was complete in 0·5 hour. The catalyst was filtered off and the solution evaporated. The oily residue distilled at 105°/0·03 mm. Yield 0·35 g. This methyl *meso*-2 : 5-dimethoxyadipate partly crystallised, and the crystals were separated on porous tile. After being recrystallised from ether–petrol, they had m. p. 52—53° (0·11 g.) (Found : C, 51·5; H, 7·8. Calc. for $C_{10}H_{18}O_6$: C, 51·3; H, 7·7%). Schmidt and Kraft (*loc. cit.*) record m. p. 53° for this substance. The porous tile employed for the separation of the crystalline material was extracted with boiling chloroform, the extract evaporated, and the residue distilled. It distilled at 100° (bath temp.)/0·03 mm. (0·2 g.) and showed $n_D^{20°}$ 1·4379. It was probably DL-methyl 2 : 5-dimethoxyadipate (Found : OMe, 52·0. Calc. for $C_{10}H_{18}O_6$: OMe, 53·0%).

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243. *The Synthesis of Piperidine Derivatives. Part III.* 5-*Phenyl*-1-*aza*bicyclo[3 : 3 : 1]*nonane.*

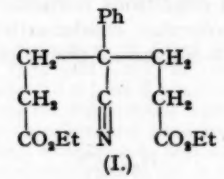
By G. M. Badger, J. W. Cook, and Thomas Walker.

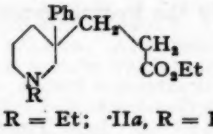
From the products of the hydrogenation of ethyl γ-cyano-γ-phenylpimelate (I) over copper chromite catalyst, *ethyl* β-(3-*phenyl*-1-*ethyl*-3-*piperidyl*)*propionate* (II) and 5-*phenyl*-1-*aza*bicyclo-[3 : 3 : 1]*nonane* (III) have been isolated; (III) has also been obtained, under certain conditions, following hydrogenation of 1 : 3 : 5-tricyano-3-phenylpentane (VII). Hydrogenation of the latter compound has also given 3-phenylpiperidine; in addition, two unidentified *bases* have been isolated and characterised.

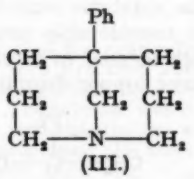
Although Adkins and Connor (*J. Amer. Chem. Soc.*, 1931, **53**, 1094) and more recently, Grundmann ("Newer Methods of Preparative Organic Chemistry," 1948, p. 120) have stated that copper chromite catalyst is ineffective for the reduction of cyanides, Barr and Cook (*J.*, 1945, 438; Part I of this series) found that γ-cyano-esters are readily reduced by hydrogenation over this catalyst to give *N*-alkylpiperidines, in which the *N*-alkyl group is provided by the alcohol used as solvent. Furthermore, Badger, Cook, and Walker (Part II; *J.*, 1948, 2011) have found that oxime-esters are likewise reduced to derivatives of *N*-alkylpiperidines, and indeed these reactions provide new and convenient methods for the preparation of compounds of this type. A preliminary report on the analgesic, antispasmodic, and local anæsthetic activity of some of the derived compounds has been published by Badger *et al.* (*Nature*, 1948, **162**, 21). In continuation of our examination of the structural features associated with biological activity of this nature, we have extended this work to the preparation of a derivative of the *iso*granatanine bridged ring system.

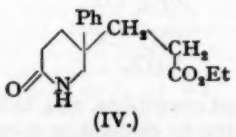
A preliminary investigation of the hydrogenation of ethyl γ-cyano-γ-phenylpimelate over copper chromite was reported by Barr and Cook (*loc. cit.*), who obtained a liquid base for which the structure 3-phenyl-1-ethyl-3-3′-ethoxypropylpiperidine (V) was tentatively suggested. This product gave no solid derivative, however, and it seemed possible that it was not completely homogeneous. The hydrogenation has now been carried out under a variety of experimental conditions, and two pure substances have been isolated and characterised.

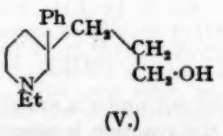
In ethanolic solution, under suitable conditions of temperature and pressure, the hydrogenation of the cyano-diester (I) over copper chromite catalyst gave *ethyl* β-(3-*phenyl*-1-*ethyl*-3-*piperidyl*)*propionate* (II) in almost theoretical yield, although in one run, a small quantity of 5-*phenyl*-1-*aza*bicyclo[3 : 3 : 1]*nonane* (III) ("phenyl*iso*granatanine") was also isolated by careful fractional distillation.

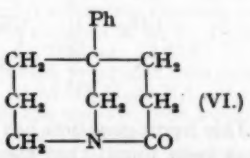

(I.)


(II, R = Et; IIa, R = H.)


(III.)


(IV.)


(V.)


(VI.)

In dioxan solution, hydrogenation gave a mixture of the two products (II) and (III). The relative proportions of the two substances varied somewhat with the experimental conditions, as did the total yield, but the bridged-ring compound (III) was normally obtained in about 20% yield.

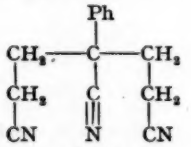
It is clear from the work of Barr and Cook (*loc. cit.*) and of Koelsch (*J. Amer. Chem. Soc.*, 1943, **65**, 2093, 2458, 2459, 2460) that the conversion of γ-cyano-esters into *N*-alkylpiperidines proceeds in four stages: (i) reduction of the cyano-group, (ii) intramolecular condensation with elimination of alcohol to give the piperidone, (iii) reduction of the piperidone to the piperidine, and (iv) alkylation by means of the alcohol used as solvent. Hydrogenations over Raney nickel were found to proceed only as far as the second stage, the piperidones being isolated. In Koelsch's experiments, the piperidones were further reduced with sodium and

butanol. Over copper chromite, however, the reaction proceeded further and *N*-alkylpiperidines were obtained directly from γ-cyano-esters. There is little doubt therefore that the hydrogenation of ethyl γ-cyano-γ-phenylpimelate (I) proceeds through the hypothetical intermediates (IV) and (II*a*). The subsequent course of the reaction is evidently governed by the experimental conditions, the ester (II*a*) reacting in two ways. In dioxan solution, part of the material undergoes a second intramolecular cyclisation with loss of alcohol, to give (VI), which on further reduction gives the bridged-ring compound (III) actually isolated. On the other hand, the hypothetical ester (II*a*) also undergoes *N*-alkylation. Indeed, in ethanolic solution, this *N*-alkylation proceeds almost exclusively, to give (II). Once *N*-alkylation has taken place the second intramolecular cyclisation to give the bridged-ring compound is effectively prevented. Even in dioxan solution the *N*-alkylation takes place to a considerable extent, although the only ethanol present in the reaction mixture is that formed by the intramolecular condensations. This provides another instance of the remarkable ease with which *N*-alkylation of piperidines may be brought about under the influence of copper chromite and high temperatures, a circumstance to which Barr and Cook have already drawn attention.

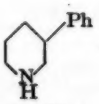
Two earlier syntheses of the *iso*granatanine ring system have been reported (McElvain and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 2738; Prelog, Heimbach, and Seiwerth, *Ber.*, 1939, **72**, 1319) but both are lengthy and give poor over-all yields. Although the yield in the present method is not good, it provides an alternative method of value for the preparation of further derivatives of this ring system. It is of interest that the recent synthesis of sparteine (Leonard and Beyler, *J. Amer. Chem. Soc.*, 1948, **70**, 2298) involves a somewhat similar intramolecular condensation of 1-carbethoxy-4-keto-3-2′-pyridylpyridocoline with hydrogen and copper chromite, in dioxan.

5-Phenyl-1-aza*bicyclo*[3 : 3 : 1]nonane (III) is a crystalline base, and it has been characterised as the *picrate* and *methiodide*. An attempt to degrade the latter by the Hofmann method was unsuccessful. Treatment with aqueous silver oxide in the usual manner eliminated the methyl group as methyl alcohol, and gave only the original base (III). Ethyl β-(3-phenyl-1-ethyl-3-piperidyl)propionate (II) was a liquid and it was characterised by the preparation of a crystalline *hydrochloride*, *oxalate*, and *picrolonate*. Hydrolysis of this ester with dilute hydrochloric acid gave the *hydrochloride* of the free acid, also converted into the *oxalate* of the methyl ester. Reduction of the ester with lithium aluminium hydride (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197) gave *3-phenyl-1-ethyl-3-3′-hydroxypropylpiperidine* (V).

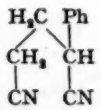
Although Huber (*ibid.*, 1944, **66**, 876) found that hydrogenation of basic cyanides over Raney nickel results in the formation of primary amines almost quantitatively, it is well known that the catalytic reduction of cyanides under other experimental conditions normally gives rise to considerable proportions of secondary amine by intermolecular condensation. It therefore seemed of interest to study the hydrogenation of 1 : 3 : 5-tricyano-3-phenylpentane (VII) over copper chromite.



(VII.)



(VIII.)



(IX.)

This hydrogenation has been carried out under a variety of different conditions, and, indeed, it has been found that the course of the reaction is unusually sensitive to changes in solvent, concentration, and the quality of catalyst. In all the experiments a large quantity of ammonia was formed, and varying quantities of 3-phenylpiperidine (VIII) were isolated, depending on the conditions. Two types of copper chromite catalyst were used. For the preparation of catalyst-A, the crude chromate (*Org. Synth.*, **19**, 31) was decomposed by heating in an electric oven at 470—500° for one hour, while for catalyst-B, the chromate was decomposed by heating over a free Bunsen flame until decomposition set in. The latter method was that originally used by Connor, Folkers, and Adkins (*J. Amer. Chem. Soc.*, 1932, **54**, 1138).

In *cyclo*hexane, over catalyst-B, hydrogenation of 1 : 3 : 5-tricyano-3-phenylpentane gave 3-phenylpiperidine, the remainder of the product being a mixture of high-boiling basic substances, which was not further examined. In dioxan, with the same catalyst, 3-phenylpiperidine was formed, and two additional substances were also isolated. The first was a

crystalline *base*, m. p. 155°, of probable formula $C_{14}H_{17-19}N_2$. It was characterised as the *picrate*, and was unchanged by boiling 70% sulphuric acid. The other product was a *base*, m. p. 247°. Analysis of this base, and of its *picrate*, indicated the presence of oxygen, which can only have arisen from the dioxan used as solvent. This seems to be the first recorded example of the decomposition of dioxan and its interaction with a reactant under such relatively mild conditions of temperature and pressure (230° and 175 atm.). According to Grundmann (*op. cit.*, p. 106), dioxan can be used for hydrogenations over copper chromite at temperatures up to 275°.

With catalyst-A, the hydrogenation proceeded differently. Varying amounts of 3-phenylpiperidine were always obtained, but under certain conditions, some phenylaza*bicyclo*nonane (III) was also isolated.

The formation of 3-phenylpiperidine in these reductions is of interest. It is unlikely that the side chain $\cdot CH_2 \cdot CH_2 \cdot CN$ is eliminated after the piperidine ring has been formed; if this were so one would expect the corresponding side chain to be eliminated in reduction of the cyano-diester (I), which is not observed. It seems more likely that 1 : 3 : 5-tricyano-3-phenylpentane (VII) itself is unstable, and dissociates in the alkaline media, and in the presence of the hydrogenation catalyst, to give the dicyanide (IX) and vinyl cyanide. The tricyanide (VII) is prepared by the Michael addition of vinyl cyanide to benzyl cyanide, and it has been demonstrated by Ingold and Powell (*J.*, 1921, **119**, 1976) that Michael reactions are reversible.

The formation of the compound (III) is perhaps even more surprising. It might be suggested that it is formed in this reaction by a mechanism similar to that usually accepted for the formation of secondary amines by hydrogenation of monocyanides, namely, the interaction of a molecule of primary amine with a molecule of imine with elimination of ammonia, followed by further reduction. It is difficult to extend this mechanism to the formation of a bicyclic compound in which the nitrogen is attached to both rings, however. On the other hand, Winans and Adkins (*J. Amer. Chem. Soc.*, 1932, **54**, 306) found that certain primary amines, in the presence of the usual reduction catalysts and at temperatures above 160°, interact to give ammonia and the corresponding secondary amine, in good yield. High temperatures were used in the present experiments on the hydrogenation of the tricyanide (VII), and in view of the proximity of the reacting groups, the latter type of mechanism seems especially applicable. Moreover Hoerr *et al.* (*J. Org. Chem.*, 1944, **9**, 201) have prepared secondary aliphatic amines from primary amines by catalytic deamination, and more recently, Martin and Martell (*J. Amer. Chem. Soc.*, 1948, **70**, 1817) have described the catalytic deamination of diethylenetriamine to piperazine at temperatures of 150° or higher.

Experimental.

Hydrogenation of Ethyl γ-Cyano-γ-phenylpimelate in Ethanol.—A solution of the cyano-diester (I; 20 g., Barr and Cook, *loc. cit.*) in absolute ethanol (400 c.c.) was shaken with hydrogen and copper chromite (10 g.) for 3 hours at 210° and 175 atm. After removal of the catalyst and the solvent, the resulting oil was treated with hydrochloric acid, in which it all dissolved. The solution was extracted once with ether, and then basified. The product was extracted with ether, and the solution was dried (Na_2SO_4), evaporated, and distilled. *Ethyl β-(3-phenyl-1-ethyl-3-piperidyl)propionate* (II) was obtained as a colourless viscous oil, b. p. 140°/0·5 mm. (Found: C, 74·9; H, 9·5; N, 4·8; OEt, 16·0. $C_{18}H_{27}O_2N$ requires C, 74·7; H, 9·4; N, 4·8; OEt, 15·55%). The *hydrochloride* formed colourless crystals, m. p. 161°, from ethyl acetate (Found: C, 66·5; H, 8·8; N, 4·5. $C_{18}H_{28}O_2NCl$ requires C, 66·3; H, 8·65; N, 4·3%); the *oxalate* formed small colourless needles, m. p. 198°, from ethanol (Found: C, 63·5; H, 7·6; N, 4·0. $C_{18}H_{27}O_2N,C_2H_2O_4$ requires C, 63·3; H, 7·7; N, 3·7%); the *picrolonate* separated from ethanol as small yellow needles, m. p. 146—148° (Found: C, 61·0; H, 6·1; N, 12·8. $C_{18}H_{27}O_2N,C_{10}H_8O_5N_4$ requires C, 60·7; H, 6·4; N, 12·65%). The pure ester, recovered from the oxalate, was boiled for 1 hour with dilute hydrochloric acid, and the mixture then evaporated in a vacuum. The resulting glass crystallised on standing. Recrystallisation from ethyl acetate containing a little ethanol gave the *hydrochloride* of the free acid, m. p. 170° (after sintering) (Found: C, 60·9; H, 8·2. $C_{16}H_{24}O_2NCl,H_2O$ requires C, 60·85; H, 8·3%). The free acid was water-soluble and was not isolated. Treatment of the acid hydrochloride with methyl alcohol and gaseous hydrogen chloride in the usual way gave an oil which was immediately converted into the *oxalate* of the methyl ester. It formed colourless needles, m. p. 192—193°, from methanol (Found: C, 62·7; H, 7·3; N, 3·9. $C_{19}H_{27}O_6N$ requires C, 62·4; H, 7·4; N, 3·8%). The ethyl ester (II; 1·0 g.) was reduced by adding an ethereal solution dropwise to a stirred solution of lithium aluminium hydride (1 g.) in anhydrous ether. After decomposition by the gradual addition of water (Nystrom and Brown, *loc. cit.*), followed by addition of dilute sulphuric acid, *3-phenyl-1-ethyl-3-3'-hydroxypropylpiperidine* (V) (0·7 g.) was isolated as a colourless viscous oil, b. p. 145°/0·1 mm. (air bath) (Found: C, 77·7; H, 10·2. $C_{16}H_{25}ON$ requires C, 77·7; H, 10·2%).

Hydrogenation of Ethyl γ-Cyano-γ-phenylpimelate in Dioxan.—The dioxan used in these experiments was purified by heating under reflux with sodium for 10 hours, followed by distillation over sodium. The cyano-diester (10 g.) in dioxan (400 c.c.) was hydrogenated over copper chromite (5 g.) for 3 hours at 210° and 175 atm. Fractional distillation of the product, which was all basic,

gave: (*a*) 5-*Phenyl*-1-*aza*bicyclo[3 : 3 : 1]*nonane* (2·5 g.) as a colourless oil, b. p. 130—135°/0·4 mm., which solidified on standing; after crystallisation from light petroleum it formed colourless needles, m. p. 64° (Found: C, 83·4; H, 9·4; N, 7·0. $C_{14}H_{19}N$ requires C, 83·6; H, 9·45; H, 7·0%); the *picrate* formed yellow needles, m. p. 178°, from ethanol (Found: C, 56·1; H, 4·7; N, 13·0. $C_{14}H_{19}N,C_6H_3O_7N_3$ requires C, 55·8; H, 5·1; N, 13·0%); the *methiodide* formed colourless needles, m. p. 236°, from ethanol (Found: C, 52·8; H, 6·3; N, 4·1. $C_{15}H_{22}NI$ requires C, 52·5; H, 6·4; N, 4·1%). (*b*) A very small quantity of ethyl β-(3-phenyl-1-ethyl-3-piperidyl)propionate, b. p. 145°/0·4 mm. It was identified by conversion into the oxalate, m. p. and mixed m. p. with the specimen prepared as above 198°. (*c*) A fraction, b. p. 240—280°/0·4 mm., distilled with some decomposition, and was not further examined.

A series of experiments under varying conditions was carried out, and the above record is of one representative experiment. Under different conditions the yield of the two products varied widely. In another experiment in which the cyano-diester (20 g.), in dioxan (400 c.c.), was reduced with hydrogen and copper chromite (5 g.) for 4 hours at 215° and 175 atm., fractional distillation gave 5-phenyl-1-aza*bicyclo*[3 : 3 : 1]nonane (2·0 g.) and ethyl β-(3-phenyl-1-ethyl-3-piperidyl)propionate (7 g.).

Attempted Hofmann Degradation of 5-*Phenyl*-1-*aza*bicyclo[3 : 3 : 1]*nonane*.—A solution of the methiodide (0·4 g.) in water, was shaken with freshly precipitated silver oxide (2 g.) for 4 hours in a tightly stoppered flask. The solid was filtered off and a test of the filtrate with silver nitrate showed the absence of iodide ions and indicated that the reaction had gone to completion. The aqueous solution, on evaporation in a vacuum, gave an oil which was heated in an oil-bath at 200° until all signs of decomposition ceased. Distillation of the product in a vacuum gave 5-phenyl-1-aza*bicyclo*[3 : 3 : 1]-nonane (0·2 g.), identified by conversion into the picrate and methiodide, and by mixed m. p. determinations with authentic specimens.

Reduction of 1 : 3 : 5-*Tricyano*-3-*phenylpentane in Dioxan*.—Many experiments under different experimental conditions were carried out. The details recorded are for typical experiments: under other conditions the yield of the various fractions varied widely.

(1) The tricyanide (VII; 10 g., Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 23) in dioxan (400 c.c.) was hydrogenated in the presence of copper chromite-A (5 g.) at 220—230° and 175 atm. for 3 hours. The resulting solution had a strong odour of ammonia. Fractionation of the basic product gave (*a*) 3-phenylpiperidine (1 g.) as a colourless oil, b. p. 85—90°/0·2 mm., (*b*) 5-phenyl-1-aza*bicyclo*-[3 : 3 : 1]nonane (1·5 g.), identified by m. p. and mixed m. p. of the free base, and of its picrate, (*c*) considerable dark brown residue which did not distil below 250°/0·2 mm. and was not further examined.

3-Phenylpiperidine was identified by conversion into its benzoyl derivative, which formed small colourless prisms, m. p. 88°, from ether–ligroin or ethyl acetate (lit. m. p. 89°). The *picrate*, prepared in ethanol, and recrystallised from glacial acetic acid, formed stout yellow needles, m. p. 209—210° (Found: C, 52·1; H, 4·6; N, 14·2. $C_{11}H_{15}N,C_6H_3O_7N_3$ requires C, 52·3; H, 4·6; N, 14·3%). Addition of excess of methyl iodide to 3-phenylpiperidine gave a vigorous reaction. After standing for some hours the excess of methyl iodide was removed. Crystallisation of the residue from ethanol gave 3-*phenyl*-1-*methylpiperidine methiodide* as colourless needles, m. p. 231° (Found: C, 49·5; H, 6·4; N, 4·3. $C_{13}H_{20}NI$ requires C, 49·2; H, 6·3; N, 4·4%). When exposed to the atmosphere in thin films, 3-phenylpiperidine was converted into the carbonate, m. p. 80—81°, which dissolved in dilute hydrochloric acid with effervescence. It decomposed on attempted crystallisation.

(2) The tricyanide (20 g.) in dioxan (400 c.c.) was reduced over copper chromite-A (9 g.) at 230° and 175 atm. for 5 hours. Fractionation gave: (*a*) 3-phenylpiperidine (3 g.) identified as the picrate, (*b*) a viscous oil, b. p. 150—200°/0·5 mm., from which no pure product could be isolated, and (*c*) a considerable residue which did not distil.

(3) The tricyanide (10 g.) in dioxan (400 c.c.) was reduced over copper chromite-B (5 g.) at 230° and 175 atm. for 4 hours. Fractionation of the product gave: (*a*) 3-phenylpiperidine (1 g.) identified as the picrate. (*b*) A colourless viscous oil (2 g.), b. p. 160°/0·5 mm., which solidified on standing; this *base* crystallised from ethyl acetate in colourless needles, m. p. 155° (Found: C, 78·3; H, 8·2; N, 12·9. *M*, Rast, 223. $C_{14}H_{18}N_2$ requires C, 78·5; H, 8·45; N, 13·1%; *M*, 214); the *picrate*, prepared in ethanol and recrystallised from glacial acetic acid, formed yellow needles, m. p. 191° (Found: C, 54·5; H, 4·5; N, 15·8. $C_{14}H_{18}N_2,C_6H_3O_7N_3$ requires C, 54·2; H, 4·75; N, 15·8%); the base was recovered unchanged after boiling with 70% sulphuric acid for 2 hours. (*c*) A few drops of a brown viscous oil, b. p. 240—260°/0·5 mm. A solution of this oil in ethanol deposited colourless needles, m. p. 247°, of a *base* (Found: C, 74·0; H, 6·7; N, 12·5%); its *picrate* crystallised from glacial acetic acid in lemon-yellow needles, m. p. 222° (Found: C, 53·4; H, 4·4; N, 15·8%).

Reduction of the Tricyanide in cyclo*Hexane*.—Hydrogenation of the tricyanide (10 g.) in *cyclo*hexane (400 c.c.) over copper chromite-B (5 g.) at 230° and 180 atm. for 3 hours gave, on fractionation, (*a*) 3-phenylpiperidine (2 g.), identified by mixed m. p. of the picrate, (*b*) a colourless viscous oil (2 g.), b. p. 160—190°/1 mm., from which no solid derivative could be isolated, and (*c*) a brown residue which did not distil below 260°.

One of us (G. M. B.) has been working with an I.C.I. Research Fellowship, and we are indebted to the D.S.I.R. for a Maintenance Allowance (to T. W.). Microanalyses have been carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

UNIVERSITY OF GLASGOW. [*Received, October 13th*, 1948.]

244. *Dissociation Energies of Carbon–Halogen Bonds. The Bond Strengths Allyl–X and Benzyl–X.*

By O. H. Gellner and H. A. Skinner.

Measurements of the heats of reaction of allyl bromide, allyl iodide, benzyl bromide, and benzyl iodide with silver nitrate in aqueous-alcoholic solution have been made. The results have been interpreted, by assuming a simplified reaction scheme, to provide rough values for the heats of formation (Q_f) of the allyl and benzyl halides. By combination of these experimental Q_f values with the D(C–H) bond dissociation energies in toluene and propylene, we derive D(R–I) bond dissociation energies as follows:

D(allyl–I) = 34·4 kcals. D(benzyl–I) = 36·5 kcals.
D(allyl–Br) = 45·5 kcals. D(benzyl–Br) = 48·5 kcals.

These values are considered to be uncertain within ±3 kcals.

Recent determinations by Szwarc (*J. Chem. Physics*, 1948, **16**, 128; *ibid.*, 1949, **17**, 284) of the bond dissociation energies of the C–H bonds, $C_6H_5{\cdot}CH_2$–H and allyl–H, in toluene and propylene, taken in conjunction with the heats of formation, $Q_f(C_6H_5{\cdot}CH_3)$ and $Q_f(CH_2{:}CH{\cdot}CH_3)$, provide values for the heats of formation (from elements in their standard states) of the benzyl and the allyl radicals. These are (see Roberts and Skinner, *Trans. Faraday Soc.*, 1949, **46**, 339): Q_f(benzyl) = −37·4 and Q_f(allyl) = −30·9 kcals. mole^{-1}.

The bond dissociation energies D(R–X) are simply related to the heats of formation Q_f(R) and Q_f(X) by the equation

$$D(\text{R–X}) = Q_f(\text{RX}) - Q_f(\text{R}) - Q_f(\text{X}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

In cases where X = Cl, Br, or I, the terms in Q_f(X) are known with high accuracy (Rossini, "Selected Tables of Chemical Thermodynamic Properties," U.S. Bureau of Standards, 1947, Tables 10-1, 11-1, 12-1). Accordingly, we may use equation (1) to estimate the bond dissociation energies of the C–halogen bonds in the benzyl and allyl halides if the heats of formation of these compounds are known.

Thomsen's measurements ("Thermochemische Untersuchungen," Vol. IV, Barth, Leipzig) of the heats of combustion of allyl chloride and allyl bromide correspond to Q_f(allyl–Cl) = −0·6 and Q_f(allyl–Br) = −11·2 kcals. mole^{-1} (unless otherwise specified, all Q_f values in this paper refer to *gaseous* states). From the heat of combustion of liquid allyl iodide, as measured by Berthelot (*Ann. Chim. Phys.*, 1900, **21**, 296), one may derive Q_f(allyl–I) ~ −33·5 kcals., but it is our view that this value is seriously in error. Relatively little is known of the heats of formation of the benzyl halides. Schmidlin's data (*ibid.*, 1906, **7**, 195) on the heat of combustion of benzyl chloride are insufficient to make a reliable estimate of Q_f(benzyl–Cl).

It is desirable that new and accurate measurements of the heats of combustion of allyl and benzyl halides should be made. Meanwhile, we are able to report the results of some measurements of the *heats of hydrolysis* of the allyl and benzyl halides, from which we can derive values for Q_f(allyl–X) and Q_f(benzyl–X). We make no claim for high accuracy in the new values reported here, for reasons given later. Nevertheless, the values we have found are consistent among themselves, and in our view, are correct within the limits of ±3 kcals.

Thermochemical Method.—Both the iodides and the bromides, benzyl–X and allyl–X, react easily and relatively quickly with silver nitrate in aqueous-alcoholic solution at room temperature. The main reaction taking place may be represented by

$$\text{RX} + \text{AgNO}_3 + \text{H}_2\text{O} \longrightarrow \text{ROH} + \text{AgX} + \text{HNO}_3 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In our thermochemical method, we have *assumed* that (2) is the only reaction. This is strictly indefensible, but from the thermochemical point of view the assumption is unlikely to lead to serious error (see p. 1146).

Representing the heats of the pairs of reactions:

$$\text{RX(liq.)} + \text{AgNO}_3\text{(aq. alc.)} + \text{H}_2\text{O(aq. alc.)} \longrightarrow \text{AgX(ppt.)} + \text{ROH(aq. alc.)} + \text{HNO}_3\text{(aq. alc.)} + Q_1 \quad . \quad . \quad . \quad . \quad (3a)$$

$$\text{HX(aq.)} + \text{AgNO}_3\text{(aq. alc.)} \longrightarrow \text{AgX(ppt.)} + \text{HNO}_3\text{(aq. alc.)} + Q_2 \quad . \quad . \quad . \quad (3b)$$

by Q_1 and Q_2, one may then write

$$\text{RX(liq.)} + \text{H}_2\text{O(aq. alc.)} \longrightarrow \text{ROH(aq. alc.)} + \text{HX(aq.)} + (Q_1 - Q_2) \quad . \quad . \quad . \quad (4)$$

From eqn. (4) we may further obtain

$$Q_f(\mathrm{RX,liq.}) = Q_f(\mathrm{ROH,aq.\ alc.}) + Q_f(\mathrm{HX,aq.}) - Q_f(\mathrm{H_2O,\ aq.\ alc.}) + (Q_2 - Q_1) \quad . \quad . \quad (5)$$

Values for the terms in Q_f on the right-hand side of eqn. (5) are known with relatively high accuracy, so that by the measurement of $(Q_2 - Q_1)$, the heat of formation of RX can be obtained. The value of Q_f(RX) so obtained is, of course, subject to the conditions that the reaction between RX and $AgNO_3$ in aqueous ethyl alcohol proceeds substantially according to eqn. (2), or that such side reactions as may occur have a similar overall molar heat of reaction to (2).

Studies of the reactions between alkyl halides and silver nitrate in aqueous and in aqueous-alcoholic solution have been made by various investigators (Nef, *Annalen*, 1899, **309**, 126; Burke and Donnan, *J.*, 1904, **85**, 555; *Bull. Soc. chim.*, 1904, **32**, 1153; Gand, Thèse, Marseille, 1939; *Bull. Soc. chim.*, 1944, **11**, 511). The main side reaction to reaction (2) is that in which the hydrolysis is accompanied by an alcoholysis:

$$\mathrm{RI + AgNO_3 + EtOH \longrightarrow ROEt + AgI + HNO_3} \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Fortunately, from the thermochemical point of view, this reaction generates a similar overall heat to the main reaction (2)—*e.g.*, in case where R = Et, the heats of reactions (2) and (6) do not differ by more than 2 kcals./mole. Moreover, we have used alcohol–water mixtures in which the molar concentration of water was roughly twice that of the alcohol. The side reaction

$$\mathrm{RI + AgNO_3 \longrightarrow RNO_3 + AgI} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

according to Gand (*loc. cit.*) does not occur in aqueous solutions to more than 5—10%, and should not, in that event, seriously interfere with the usefulness of equation (5).

An independent check on the validity of the assumed thermochemical method has been obtained by study of the reactions in which RI = CH_3I and C_2H_5I. In these cases, the values of Q_f(RI) are known, from independent studies (Carson, Hartley, and Skinner, *Proc. Roy. Soc.*, 1949, **195**, *A*, 500; Hartley and Skinner, unpublished results), within relatively small limits. The values found by use of equation (5), and the measured heats of hydrolysis, agreed within ± 2 kcals. with those obtained by more reliable methods. Accordingly, we feel justified in claiming that the thermochemical method we have used gives results which are reliable within the limits ± 3 kcals., although our values require independent confirmation.

Experimental.

The reactions were initiated by breaking a phial containing the alkyl halide into a solution of silver nitrate in aqueous alcohol, contained within a Dewar vessel calorimeter of simple design, similar to that described by Bichowsky (*J. Amer. Chem. Soc.*, 1923, **45**, 2225). The temperature rise was followed on a Beckmann thermometer, and after a suitable time of reaction (usually 10 minutes with the benzyl halides, and about 30 minutes with the allyl halide reactions), reaction was terminated by flooding the reaction mixture with an excess of standard potassium thiocyanate solution. The extent of reaction was determined by back titration of the excess of thiocyanate. In general, 2—4 g. of alkyl halide were used in each run, and 300 c.c. of aqueous-alcoholic silver nitrate were contained within the Dewar vessel.

The results obtained with allyl and benzyl iodide and bromide are set out in the Table I (Q_1 is in kcals./mole; W.E. = water equivalent of calorimeter in cals./°c.).

The ΔT values given are corrected for small solution heats, due to the heat of solution of the *unreacted* alkyl halide in the reaction mixture.

The heat quantities Q_2 (equation 3*b*) were measured by breaking phials containing concentrated hydriodic or hydrobromic acid into the aqueous-alcoholic silver nitrate solution. Since part of the observed temperature rise was due to the addition of the water admixed with the acid, corrections were made for this spurious heat effect. The results are summarised in Table II. The Q_2 values in the aqueous alcohol mixture (200 c.c. EtOH; 100 c.c. H_2O) are thus rather less (by *ca.* 2 kcals.) than in the purely aqueous solution.

The term $(Q_2 - Q_1)$ in eqn. (5), as found from these experiments, has the values: C_3H_5Br(liq.), −3·7; C_3H_5I(liq.), 2·1; CH_2PhBr(liq.), −1·9; CH_2PhI(liq.), 3·0 kcals.

The remaining terms in eqn. (5) were taken from published heats of formation, with some small adjustments to take care of small solution heats that were measured wherever necessary. These terms (in kcals.) are summarised below;

Q_f(HX, aq.)	Q_f(HI,7H_2O)	= 12·1 [1]	Q_f(ROH, aq. alc.)	Q_f(C_2H_5·OH)	= 40·3 [2]
	Q_f(HBr,11H_2O)	= 27·8 [1]		Q_f(CH_2Ph·OH)	= 36 [3]
Q_f(H_2O, aq. alc.)	Q_f	= 68·5 [1]			

[1] Rossini, *op. cit.*, Tables 11-2, 12-2.
[2] Dolliver, Gresham, Kistiakowsky, Smith and Vaughan,, *J. Amer. Chem. Soc.*, 1938, **60**, 440.
[3] Stohmann, *Z. physikal. Chem.*, 1890, **6**, 334.

Substituting these various values into eqn. (5), we obtain the following (in kcals./mole^{-1}):

Q_f(C_2H_5-Br, liq.) = − 4·1	Q_f(CH_2Ph-Br, liq.) = − 6·6
Q_f(C_2H_5-I, liq.) = − 14·0	Q_f(CH_2Ph-I, liq.) = − 17·4

TABLE I.

(a) *Allyl bromide and silver nitrate (aqueous alcohol).*

C_3H_5Br added (g.-mole).	C_3H_5Br reacted (g.-mole).	ΔT.	W.E.	Q_1.	C_3H_5Br added (g.-mole).	C_3H_5Br reacted (g.-mole).	ΔT.	W.E.	Q_1.
0·0142	0·0102	1·14°	211	23·6	0·0166	0·0121	1·285°	211	22·4
0·0166	0·0120	1·295	213	22·8	0·0166	0·0120	1·315	211	23·1

Mean-value of Q_1 = 23·0 kcals. Max. deviation from mean = ± 0·6 kcal. Average reaction time ~40 mins.

(b) *Allyl iodide and silver nitrate (aqueous alcohol).*

C_3H_5I added (g.-mole).	C_3H_5I reacted (g.-mole).	ΔT.	W.E.	Q_1.	C_3H_5I added (g.-mole).	C_3H_5I reacted (g.-mole).	ΔT.	W.E.	Q_1.
0·0154	0·0136	1·53°	211	23·7	0·0154	0·0142	1·56°	211	23·2
0·0154	0·0141	1·57	211	23·5	0·0154	0·0135	1·505	211	23·5

Mean value of Q_1 = 23·5 kcals. Max. deviation from mean = ± 0·3 kcal. Average time of reaction = ~ 30 mins.

(c) *Benzyl bromide and silver nitrate (aqueous alcohol).*

CH_2PhBr added (g.-mole).	CH_2PhBr reacted (g.-mole).	ΔT.	W.E.	Q_1*.	CH_2PhBr added (g.-mole).	CH_2PhBr reacted (g.-mole).	ΔT.	W.E.	Q_1*.
0·0164	0·0147	1·50$_5$°	213	21·8	0·0163	0·0144	1·45$_5$°	213	21·5
0·0166	0·0146	1·48	,,	21·6	0·0152	0·0137	1·37$_5$	,,	21·4

* The benzyl bromide was dissolved in 5 c.c. of alcohol, and then introduced into the reaction mixture. The value of Q_1* includes a solution heat, and the true Q_1 for benzyl bromide (liq.) is 0·4 kcal. less than Q_1*.

Mean Q_1* = 21·6 kcals. Mean Q_1 = 21·2 kcals. Max. deviation from mean = ± 0·2 kcal. Average reaction time = ~ 10 mins.

(d) *Benzyl iodide and silver nitrate (aqueous alcohol).*

CH_2PhI added (g.-mole).	CH_2PhI reacted (g.-mole).	ΔT.	W.E.	Q_1*.	CH_2PhI added (g.-mole).	CH_2PhI reacted (g.-mole).	ΔT.	W.E.	Q_1*.
0·0149	0·0115	1·27°	213	23·5	0·0157	0·0129	1·41°	213	23·3
0·0150	0·0134	1·46	213	23·2	0·0156	0·0134	1·43	213	22·7
0·0145	0·0130	1·44$_5$	213	23·8					

* The iodide was dissolved in 5 c.c. of alcohol, and then introduced into the reaction mixture. The value of Q_1* thus includes this heat of solution. The true Q_1 for benzyl iodide (liq.) is less than Q_1* by 0·7 kcal.

Mean Q_1* = 23·3 kcals. Mean Q_1 = 22·6 kcals. Max. deviation from mean : ±0·5 kcal. Average reaction time = 10 mins.

TABLE II.

	Q_2 (obs.), kcals.		Q_2 (obs.), kcals.
(1) $HI(7H_2O) + AgNO_3$ (750H_2O)	27·5	(2) $HBr(11H_2O) + AgNO_3$ (750 H_2O)	21·2
(1*a*) $HI(7H_2O) + AgNO_3$ (aq. alc.) ...	25·6	(2*a*) $HBr(11H_2O) + AgNO_3$ (aq. alc.)	19·3

Discussion.—The heats of vaporization of the allyl and benzyl halides do not appear to have been measured. It is probable, however, that those of the allyl halides are *ca.* 8 kcals., and those of the benzyl halides *ca.* 9 kcals. Assuming these values, we can obtain Q_f(RX), and the bond dissociation energies D(R–X), as follows (in kcals.) :

	Q_f(R–X).	D(R–X).		Q_f(R–X).	D(R–X).
C_3H_5–Br	−12·1	45·5	CH_2Ph–Br	−15·6	48·5
C_3H_5–I	−22·0	34·4	CH_2Ph–I	−26·4	36·5

The uncertainty in these figures—as discussed earlier—is estimated at *ca.* ±3 kcals.

We may note that our value for $Q_f(C_3H_5$–Br) agrees reasonably closely with that derived from Thomsen's heat of combustion. With allyl iodide, however, there is a large discrepancy between our value and $Q_f(C_3H_5$–I) as derived from Berthelot's data.

The D(R–I) values (R = allyl or benzyl) obtained by Butler and Polanyi (*Trans. Faraday Soc.*, 1943, **39**, 19) from kinetic studies of rates of pyrolysis run some 4—5 kcals. higher than the

values given here. However, more extensive studies on the benzyl iodide and allyl iodide pyrolyses by Horrex and Szwarc (in the press; see also Szwarc, *loc. cit.*), and by Szwarc and Shaw (private communication) have since been made, and are indicative of lower values for the bond dissociation energies in these compounds than were first reported.

The authors wish to express their thanks to Dr. M. Szwarc, who first suggested that the reactions studied here might prove useful for thermochemical study, and who supplied us with samples of the allyl and benzyl halides.

THE UNIVERSITY, MANCHESTER. [*Received, October 19th*, 1948.]

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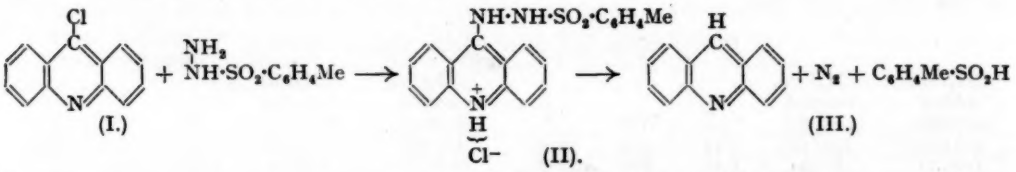
245. *Acridine Syntheses and Reactions. Part V. A New Dehalogenation of 5-Chloroacridine and its Derivatives.*

By ADRIEN ALBERT and RICHARD ROYER.

5-Chloroacridine and its derivatives have been dehalogenated by condensing them with toluene-*p*-sulphonylhydrazide and heating the resulting adducts with dilute alkalis. This reaction makes possible for the first time the transformation of those 5-chloroacridines (and hence acridones), which have easily reducible groups (*e.g.*, ·CN and ·NO_2), into the corresponding acridines.

The formerly difficult steps of chlorinating an aminoacridone to an amino-5-chloroacridine, followed by replacement of the chlorine atom, have been satisfactorily accomplished for 3-aminoacridone by first converting it into the carbethoxy-derivative.

IT would be valuable to have a standard method for replacing an active chlorine atom in heterocyclic compounds by hydrogen without the use of hydrogenation or reducing agents. In this way, the hydrogenation of the nucleus could be avoided and the integrity of such easily reducible groups as ·NO_2 and ·CN preserved.



(I.) (II). (III.)

The reductive dehalogenation of 4-chloro-3-nitro-6 : 7-benzquinoline, recently accomplished by means of toluene-*p*-sulphonylhydrazide (Albert, Brown, and Duewell, *J.*, 1948, 1284), seems to be such a general method, and the present work describes its successful application in the acridine series. As 5-chloroacridines can be prepared quantitatively from the corresponding acridones by the action of phosphorus oxychloride, it can also be used to transform acridones into acridines. The only other recorded attempt to perform a reaction similar to (II ⟶ III) in a heterocyclic system was made by Dewar (*J.*, 1944, 619) on 4-chloro-8-nitro-6-methoxyquinazoline. The yield was only 8%, but the conditions used were different from those worked out here.

5-Chloroacridine (I) was mixed with toluene-*p*-sulphonylhydrazide in chloroform solution. Next day, the adduct, 5-N′-(*toluene*-p-*sulphonyl*)*hydrazinoacridine hydrochloride* (II) was filtered off and heated with alkali, in aqueous ethylene glycol, at 97° for 2 hours. The products (III) of this reaction are acridine, nitrogen, and toluene-*p*-sulphinic acid. The sulphinic acid was identified by conversion into 2 : 4-dinitrophenyl *p*-tolyl sulphone (m. p. and mixed m. p. confirmed). The yields of dehalogenated acridines from 5-chloroacridine and also from six substituted 5-chloroacridines are shown in the annexed table. The maximal yields range from 40 to 73% calculated on the chloroacridine taken. The ratio of alkali (about a tenfold excess) to adduct was not varied, but the volume of solvent was changed, thus maintaining different concentrations of hydroxyl ion. Sodium hydroxide is too destructive for the cyano- and nitro-derivatives, and in these cases the best yields were obtained with very dilute sodium carbonate.

Results with other alkalis (including glycine-, *cyclo*hexylamine- and piperidine-buffers) and solvents (including water) were far inferior.

2-*Chloroacridine* was obtained in two interconvertible modifications, m. p. 129° and 134°, respectively, thus resembling 1-chloroacridine (forms, m. p. 79° and 90°; Clemo, Perkin, and Robinson, *J.*, 1924, **125**, 1751). The differences in m. p. of about 10° between the 1-, 2-, 3- and

4-chloro-5-aminoacridines prepared by Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169) and by Wilkinson and Finar (*J.*, 1946, 115) are due to the same effect.

This reaction makes it possible for the first time to prepare acridines with cyano-substituents in the benzene rings; *3-cyanoacridine* was thus obtained. Use of stronger alkali led also to *acridine-3-carboxyamide*, identified by hydrolysis to acridine-3-carboxylic acid (Albert and Goldacre, *J.*, 1946, 710). The present reaction is also of special value for the preparation of nitroacridines. These have been made previously by nitrating acridine or by the ring-closure of nitrodiphenylamine-2-aldehydes, but neither method can be recommended for preparative purposes.

Transformation of 5-chloroacridines into the corresponding acridines through the N'-toluenesulphonylhydrazide adducts (for conditions see p. 1148).

5-Chloro-acridine derivative.	Yield of adduct, %.	Acridine derivative.	Yield, % (calc. on adduct), and m. p. NaOH. 0·25N.	0·5N.	N.	2N.	Na_2CO_3. 0·125N.	0·25N.	N.	Highest recorded m. p.
(Unsubstituted)	92 (crude)	(Unsubstituted)	58 105—107°	70 106—108°	70 105—106°	79 104—106°	—	—	—	110—111°
(Unsubstituted)	48 (pure)	(Unsubstituted)	61 + 20[a] 105—110°	85 108—110°	93 108—110°	78 100—102°	—	—	—	110—111
2-Chloro-	92 (crude)	2-chloro-[e]	75 128—129°	76 128—129°	77 128—129°	76 128—129°	—	—	—	129
3-Cyano-	100 (crude)	3-cyano-	—	0	—	—	65 206—207°	53 203—205°	15[c] 201—203°	209 —
2-Nitro-	97 (crude)	2-nitro-	—	0	—	—	54 175—177°	28 174—177°	0	— 183
3-Nitro-	99 (pure)	3-nitro-	—	0	—	—	52 209—211°	37 204—207°	0	— 215
3-Urethano-	78 (crude)	3-amino-	—	—	51[b] 211—212°	51[b] 209—211°	—	—	25[d] 201—204°	— 213—214
1 : 3-Dimethyl-	80 (crude)	1 : 3-dimethyl-	67 67—68°	84 68—69°	87 65—67°	84 64—66°	—	—	—	— 71

[a] The extra 20% was obtained by a further acid treatment as described in the text.
[b] Complete removal of the carbethoxy-group occurred during the reaction.
[c] Acridine-3-carboxyamide was also obtained in 42% yield.
[d] A subsequent hydrolysis with N-sodium hydroxide was performed to remove the carbethoxy-group.
[e] The crude preparations were converted without loss into a higher-melting form (cf. p. 1151).

When easily reducible groups are absent, an alternative method for dehalogenating 5-chloroacridines is known, viz., catalytic hydrogenation over Raney nickel, followed by oxidation with chromic acid (Albert and Willis, *J. Soc. Chem. Ind.*, 1946, **65**, 26). For the purposes of comparison, 5-chloroacridine and 5-chloro-1 : 3-dimethylacridine were converted by this process into acridine and 1 : 3-dimethylacridine, respectively. The yields were approximately the same as those obtained by the new method.

The present reaction has a formal similarity to the McFadyen and Stevens reaction for converting acids into aldehydes (*J.*, 1936, 584), but the mechanism of the latter reaction is not known and the yields are nil when a nitro-group is situated *para* to the carbon which is to receive the hydrogen atom (Niemann and Hays, *J. Amer. Chem. Soc.*, 1943, **65**, 482). However, this ban did not operate in the present case (cf. 2-nitroacridine). Because the present reaction requires alkali and does not occur in acid solution, the necessity for the formation of an anion can be assumed. Those examples with electron-attracting substituents (·Cl, ·NO_2, ·CN) would be able to retain their anion at a higher hydrogen-ion concentration than the other examples; this explains why the dimethyl and the unsubstituted adducts were more sensitive to a fall in pH (see Table). The reaction cannot be described as a reduction, because easily reducible groups (·NO_2, ·CN) survive it. It may be regarded essentially as the thermal decomposition of an anion of (II).

The unsubstituted adduct (II) formed a small amount (*ca.* 20%) of an acid- and alkali-soluble

by-product in 0·25N-sodium hydroxide. This could be transformed into acridine by acidifying with hydrochloric acid and evaporating to dryness in a vacuum at 120° (see Table). No such by-product was obtained in 0·5N-sodium hydroxide, but at a higher temperature (120°) a solution of sodium hydroxide (0·5N. or 2N.) in ethylene glycol produced traces of 5-aminoacridine (identified by mixed m. p. with an authentic specimen) as well as acridine.

An old problem in acridine chemistry, the chlorination of aminoacridones to 5-chloro-*x*-aminoacridines has usually been attacked after first protecting the amino-group by acetylation. This is not very successful, and it was found that 5-chloro-3-acetamidoacridine is highly unstable and gives only a 35% yield of 3 : 5-diaminoacridine even when dissolved in dry phenol and treated with a stream of dry ammonia for an hour at 120°. On the other hand, *5-chloro-3-urethanoacridine*, readily prepared by the action of ethyl chloroformate on 3-aminoacridone, was much more stable; it gave a 60% yield of 3 : 5-diaminoacridine even when no special drying precautions were taken and, when treated with toluene-*p*-sulphonylhydrazide, it was readily converted into 3-aminoacridine.

Experimental.

(Microanalyses are by The Wellcome Chemical Works, Dartford, The Wellcome Chemical Research Laboratories, Beckenham, and Messrs. Weiler and Strauss.)

Toluene-p-*sulphonylhydrazide*.—To toluene-*p*-sulphonyl chloride (9·52 g.; 0·05 mol.) in benzene (25 ml.) hydrazine hydrate (10 g. of 50%; 0·1 mol.) was added and the whole was shaken by hand until heat was no longer evolved (15 minutes) and then mechanically for 2 hours. The product was filtered off, washed with cold water (25 ml.) and then with light petroleum (15 ml.), and dried to constant weight at 75°. The crude product (95%, m. p. 105—108°) was recrystallised from 15 parts of water (73% recovery) or 5 parts of chloroform (67% recovery) and then melted at 112°. This substance has previously been prepared by Freudenberg and Blümmel (*Annalen*, 1924, **440**, 45), who did not give sufficiently detailed directions.

Adducts [5-N′-(*toluene*-p-*sulphonyl*)*hydrazinoacridine hydrochlorides*, e.g., II]. Cold saturated chloroform solutions of toluene-*p*-sulphonylhydrazide and the relevant 5-chloroacridine were mixed and set aside for 1—2 days. When electron-attracting substituents were present (·CN, ·NO_2, ·Cl), a precipitate was formed almost quantitatively; this was filtered off and air-dried. In the other cases, a fast stream of dry hydrogen chloride was bubbled through the solution for about 10 seconds and the precipitate was filtered off a day later. The adducts are yellow, infusible substances and attempts to liberate the base always resulted in decomposition. The following examples were analysed. *5-N′-(Toluene*-p-*sulphonyl)-hydrazinoacridine hydrochloride* was recrystallized three times from methanol containing hydrogen chloride (0·01N.) and dried in a vacuum at 20° (Found: C, 59·1; H, 4·8; N, 10·7; Cl, 8·9. $C_{20}H_{18}O_2N_3ClS$ requires C, 60·0; H, 4·5; N, 10·5; Cl, 8·9%). *3-Nitro-5-N′-(toluene*-p-*sulphonyl)hydrazino-acridine hydrochloride* was analysed as first precipitated (Found: C, 53·95; H, 3·85; Cl, 8·2. $C_{20}H_{17}O_4N_4ClS$ requires C, 54·0; H, 3·85; Cl, 8·0%). *5-N′-(Toluene*-p-*sulphonyl)hydrazino-1 : 3-dimethyl-acridine hydrochloride* was recrystallized from methanolic hydrogen chloride as above (Found: N, 9·7. $C_{22}H_{22}O_2N_3ClS$ requires N, 9·8%).

Decomposition of the Adducts.—N-Sodium hydroxide solution was made by dissolving sodium hydroxide (4 g.) in water (30 ml.) and ethylene glycol (70 ml.), the 2N- and 0·5N-solutions by using half and double these amounts of fluids, respectively. The finely powdered adducts (0·005 mol.) were added to these solutions and the mixtures were heated in a boiling water-bath for 2 hours (3 hours if evolution of gas was incomplete). Any undissolved lumps were broken up from time to time. The reaction mixture was poured into twice its volume of water and refrigerated. The precipitate was filtered off and extracted with N-hydrochloric acid. The extract was poured into an excess of aqueous ammonia and the required acridine was filtered off. Except for the example referred to above, no further material was recoverable by removing the water and glycol in a vacuum after acidification.

5-Chloro-1 : 3-dimethylacridine.—This was obtained by the action of phosphorus oxychloride on 2′ : 4′-dimethyldiphenylamine-2-carboxylic acid according to the general method described by Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169). It formed pale yellow crystals from benzene, m. p. 114° (Kaufmann, *Annalen*, 1894, **279**, 281, gave m. p. 108°) (Found: C, 74·5; H, 5·1. Calc. for $C_{15}H_{12}NCl$: C, 74·5; H, 5·0%).

5-Chloro-3-urethanoacridine.—To 3-aminoacridone (3·3 g.) and diethylaniline (2·4 g.) in boiling absolute alcohol (240 ml.), was added freshly distilled ethyl chloroformate (1·7 g.). After being heated under reflux for 30 minutes, the solution was concentrated to one-third of its volume and poured into N-hydrochloric acid (50 ml.). 3-Urethanoacridone was obtained (in 95% yield) as a greenish-yellow solid, decomposing at *ca.* 355° and only slightly soluble in the usual organic solvents. This acridone (1·5 g.) and phosphorus oxychloride (7·5 ml.) were heated under reflux for 1 hour and then refrigerated; the orange solid was filtered off and decomposed by ice and ammonia, giving *5-chloro-3-urethanoacridine* in 87% yield. It formed yellow crystals, m. p. 183°, from benzene (Found: C, 63·5; H, 4·25. $C_{16}H_{13}O_2N_2Cl$ requires C, 63·9; H, 4·35%).

3 : 5-*Diaminoacridine*.—The last-mentioned chloro-compound was aminated in phenol, by the general method of Albert and Gledhill (*loc. cit.*), in 87% yield. The amino-compound (0·3 g.) and hydrogen bromide (47% w/w; 5 ml.) were heated under reflux for 2½ hours and then evaporated to dryness. The resulting solid was dissolved in water, and the solution was made neutral to litmus, filtered from weakly basic material, and poured into an excess of 2·5N-sodium hydroxide. The precipitate of 3 : 5-diaminoacridine was crystallized from chlorobenzene, forming orange crystals, m. p. 245° (decomp., sealed tube); yield, 68% (Found: C, 74·5; H, 5·3; N, 19·6. Calc. for $C_{13}H_{11}N_3$: C, 74·6; H, 5·3; N, 20·1%). Reduction of 3-nitro-5-aminoacridine by the method of Albert and Ritchie (*J.*, 1943, 458) gave the same

substance (m. p. and mixed m. p.). The previous workers gave a lower m. p. (229—230°, from dilute alcohol).

2-Chloroacridine was obtained as pale yellow crystals, m. p. 129° or 134° from benzene (by supersaturation) (Found: C, 73·0; H, 3·8; N, 6·6; Cl, 16·7. $C_{13}H_8NCl$ requires C, 73·1; H, 3·8; N, 6·6; Cl, 16·6%). This substance could not be prepared by hydrogenating 2 : 5-dichloroacridine over Raney nickel at 20°, as both chlorine atoms tended to be replaced.

3-Cyanoacridine was obtained as pale yellow crystals, m. p. 209°, from chlorobenzene (by supersaturation) (Found: C, 82·2; H, 3·95; N, 13·7. $C_{14}H_8N_2$ requires C, 82·3; H, 3·95; N, 13·7%).

Acridine-3-carboxyamide was obtained as cream-coloured crystals, m. p. 243° (from chlorobenzene) (Found: C, 75·6; H, 4·3. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5%).

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WELLCOME RESEARCH INSTITUTION, LONDON, N.W.1. [*Received, October 29th*, 1948.]

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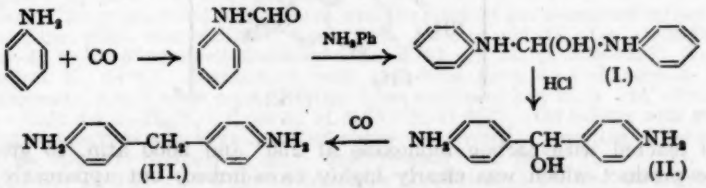
246. *High-pressure Reactions of Carbon Monoxide. Part I. Reaction with Primary Arylamines.*

By G. D. BUCKLEY and N. H. RAY.

Carbon monoxide reacts with aniline in the presence of a trace of hydrogen chloride at 250° and 2500—3000 atm. to give a polymeric product consisting of aniline residues linked by methylene and/or carbinol groups in the *o*- and *p*-positions. The probable course of this reaction has been determined. The introduction of substituents into the reactive *o*- and *p*-positions of the aniline molecule affects the nature of the products; amines having one such substituent (*e.g.*, *o*-toluidine, *p*-bromoaniline) give products similar to the products from aniline; amines having two such substituents (*e.g.*, the *m*-xylidines) give diformamidodiarylmethanes; 2 : 4 : 6-trisubstituted anilines (*e.g.*, mesidine) are merely converted into their *N*-formyl derivatives. Under similar conditions methylaniline yields *N*-methylformanilide, and dimethylaniline fails to react.

SOME 15 years ago it was observed in these laboratories that carbon monoxide reacted with aniline in presence of an acid catalyst at high temperature and pressure to give a basic product of high molecular weight. The observation was not pursued at that time, but we have recently studied the reaction in some detail and determined the nature of the products.

It was found that, when aniline containing a small amount of aniline hydrochloride was heated to 250° with carbon monoxide at 3000 atm. pressure, a reaction took place giving carbon dioxide and a brown amorphous solid, the pressure falling sharply. Little reaction occurred at 200° or at 2000 atm. or in absence of the hydrochloride. The solid product contained varying amounts of oxygen, and the whole of the nitrogen was present in the form of primary amino-groups, which were determined by diazotisation. It was separable into two fractions. The one, soluble in N- but insoluble in 3N-hydrochloric acid, was oxygen-free and had the empirical formula C_7H_7N; it therefore seemed probable that it consisted of aniline residues linked by methylene groups, presumably in the *o*- and *p*-positions. The other fraction, soluble in 0·1N- but not in N-hydrochloric acid, appeared to be a substance of similar structure, in which some of the methylene groups were replaced by carbinol; although the whole of the nitrogen was present as primary amino-groups, the material contained oxygen ranging from 4·4 to 14·5% in different samples. Further data on the reaction were obtained by carrying out experiments in which the pressure was maintained at 2700—3000 atm. by the continual introduction of fresh carbon monoxide, and the reaction was stopped and samples withdrawn for examination at regular intervals. After 10 hours the reaction mixture was still liquid and completely soluble in 3N-hydrochloric acid; at this stage it contained 25% of unchanged aniline, and *pp'*-diaminodiphenylmethane was identified among the reaction products. During the next 5 hours it was

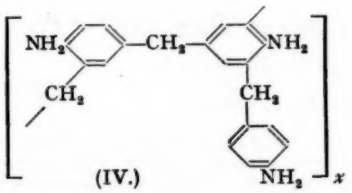


largely converted into the mixture of acid-soluble polymers described above, and during the following 10 hours this slowly reacted further to form an infusible, insoluble, cross-linked

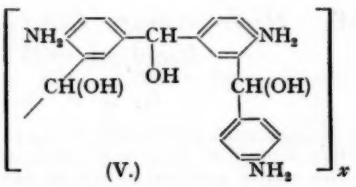
material having no basic properties. It is considered likely that the initial step in the reaction is the interaction of aniline and carbon monoxide to give formanilide, which, it is postulated, may then react with more aniline to give the unstable intermediate (I) which undergoes rearrangement to *pp'*-diaminodiphenylcarbinol (II) under the influence of the acid catalyst; the carbinol is then reduced by carbon monoxide to *pp'*-diaminodiphenylmethane (III).

Both the diarylmethane and the carbinol contain unsubstituted positions ortho- to the amino-groups, and can therefore react further with more carbon monoxide to give polymeric *products* of types (IV) and (V) and ultimately a completely cross-linked structure.

The behaviour of substituted anilines was consistent with this interpretation. Dimethylaniline failed to react with carbon monoxide under the conditions used for aniline, and methylaniline gave only *N*-methylformanilide. Primary amines having one substituent in the *o*- or *p*-position (*o*-toluidine, *p*-toluidine, *p*-bromoaniline, ethyl anthranilate) gave products

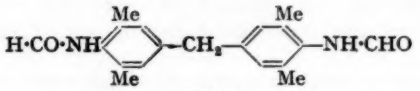


(IV.)

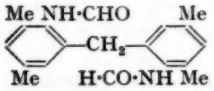


(V.)

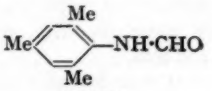
closely resembling those obtained from aniline, but no evidence of cross-linking was observed. *vic.-m*-Xylidine, having only one reactive position, gave 4 : 4'-*diformamido*-3 : 3' : 5 : 5'-*tetramethyldiphenylmethane* (VI) as the sole product, and *as-m*-xylidine similarly gave 2 : 2'-*diformamido*-3 : 3' : 5 : 5'-*tetramethyldiphenylmethane* (VII); in the latter case, however, a considerable amount of formo-*as-m*-xylidide was also produced, presumably owing to the lower reactivity of the *o*- compared with the *p*-position. Mesidine, having no free *o*- or *p*-positions, gave only formomesidide (VIII).



(VI.)



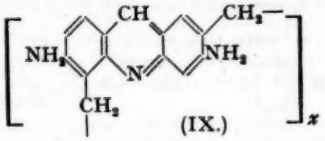
(VII.)



(VIII.)

A curious feature is the isolation of free amines only from aniline and the monosubstituted anilines even when the reaction was stopped at the diaminodiphenylmethane stage, whereas mesidine and the xylidines gave exclusively formamido-compounds. This indicates that the initial formylation step in the reaction cycle is slow and that the two following steps to give the diaminodiarylcarbinol are relatively rapid. The final step in the cycle, reduction of carbinol to methylene, must also be slow since oxygen-containing compounds of high molecular weight were invariably present, sometimes in high proportion, in the products from aniline and monosubstituted anilines.

The reaction has been applied to two diamines, both of which showed somewhat different behaviour. *m*-Phenylenediamine yielded an acid-soluble product very similar in general properties to the products from aniline, but only half of the total nitrogen was present as primary amino-groups; it is possible that the polymer in this case is built up of 2 : 8-diaminoacridine residues linked by methylene groups (IX), since Albert (*J.*, 1941, 121, 484; 1947, 244) has shown that *m*-phenylenediamine reacts with formic acid to give 2 : 8-diaminoacridine.



(IX.)

Benzidine reacted with carbon monoxide at 250° and 3000 atm. to give an infusible, acid-insoluble product which was clearly highly cross-linked, but apparently contained free amino-groups since it absorbed mineral acids from dilute solution and could be acetylated.

This work is the subject of Brit.Pat.Appln. 22709/46.

Experimental.

(Microanalyses by Dr. A. F. Colson. All m. p.s are uncorrected.)

Reaction of Aniline with Carbon Monoxide.—(a) *Acid-soluble products.* Aniline (40 g.) and hydrochloric acid (0·2 c.c., 35%) were charged into a stainless-steel, high-pressure autoclave of 80 c.c. capacity, fitted with a magnetically operated reciprocating stirrer. Carbon monoxide was compressed in to a pressure of 1000 atm. and the temperature was raised to 250°. The pressure was then raised to 3000 atm. by introduction of more carbon monoxide, and the mixture was stirred at 250° for 23 hours during which time the pressure slowly fell to 2200 atm. The residual gas contained 12·65% of carbon dioxide. After cooling, and releasing the pressure there remained 50 g. of a pale brown solid, completely soluble in 0·2N-hydrochloric acid (Found: C, 75·6; H, 6·1; N, 11·6%; acetyl value 269 mg. KOH/g.; titration with 0·1N-sodium nitrite gave NH_2, 13·35%). In subsequent experiments the products contained less oxygen.

The crude product (130 g.) was stirred with 3N-hydrochloric acid (500 c.c.) at 20° to remove low-molecular-weight bases, and the residue (125 g.) was then extracted four times with cold N-hydrochloric acid (4 × 1 l.). The extracts were made alkaline by addition of dilute sodium hydroxide solution, and the precipitate was collected, washed with water, and dried at 60°, giving a fawn powder (81 g.), m. p. 110—120° [Found: C, 79·9; H, 6·2; N, 13·3 $(C_7H_7N)_n$ (IV) requires C, 80·0; H, 6·65; N, 13·35%]. The residue insoluble in N-hydrochloric acid was extracted four times with cold 0·1N-hydrochloric acid (4 × 1 l.), leaving a dark brown powder (9 g.) insoluble in all concentrations of acid. The base, isolated from the extract as described above, was a fawn powder (35 g.), m. p. 160—170° (Found: C, 78·0; H, 5·6; N, 12·0%). A fraction similarly obtained from a product of higher initial oxygen content had C, 68·9; H, 5·9; N, 11·6%. Both the acid-soluble fractions were diazotised on treatment with nitrous acid, and the diazonium salts gave red lakes with alkaline β-naphthol.

(b) *Acid-insoluble products.* Aniline (40 g.) and hydrochloric acid (0·2 c.c., 35%) were caused to react with carbon monoxide at 250° as described above, but the pressure was held at 2700—3000 atm. by continual addition of fresh carbon monoxide, and at 5-hourly intervals the vessel was cooled and the pressure released and samples were removed for examination, with the following results:

Time, hrs.	Appearance.	% Soluble in 3N-HCl.	% Insoluble in 3N-HCl, soluble in N-HCl.	% Insoluble in N-HCl, soluble in 0·1N-HCl.	% Acid-insoluble.
5	Mobile liquid	100			
10	Viscous liquid	100			
15	Solid	6·8	67·5	6·0	20
20	Solid	0	3·3	6·6	86·5
25	Solid	0	0	0	100

The acid-insoluble product was a dark brown powder insoluble in organic solvents. It was unattacked by boiling concentrated hydrochloric acid or alcoholic potassium hydroxide, had no detectable basic properties, and on heating decomposed without melting (Found: C, 73·4; H, 6·5; N, 10·3. $C_{17}H_{14}O_3N_2$ requires C, 73·4; H, 5·05; N, 10·1%).

(c) *4 : 4′-Diaminodiphenylmethane.* Aniline (40 g.) and hydrochloric acid (0·2 c.c., 35%) were treated with carbon monoxide at 250° and 3000 atm. pressure for 10 hours, during which the pressure fell to 2410 atm. The product, a viscous liquid, was distilled under reduced pressure, giving unchanged aniline (10 g.) and a fraction (5 g.), b. p. 160—200°/6 mm., which crystallised. Recrystallisation from aqueous methanol gave colourless crystals of 4 : 4′-diaminodiphenylmethane, m. p. 94° (Found: C, 78·5; H, 6·9; N, 13·9. Calc. for $C_{13}H_{14}N_2$: C, 78·8; H, 7·05; N, 14·15%). Reaction with acetic anhydride gave the diacetyl derivative, m. p. 219° (Found: C, 72·5; H, 6·7; N, 9·4. Calc. for $C_{17}H_{18}O_2N_2$: C, 72·35; H, 6·4; N, 9·9%).

Reaction of Substituted Anilines with Carbon Monoxide.—In all experiments the amine (40 g.) and hydrochloric acid (0·2 c.c., 35%) were heated to 250° in an 80-c.c. vessel, and carbon monoxide was compressed in to 3000 atm. The reaction was continued with stirring for 23 hours without further addition of carbon monoxide.

Methylaniline. The pressure fell to 2700 atm. The product, a dark liquid, was distilled under reduced pressure, giving *N*-methylformanilide (20 g.), b. p. 95°/4 mm., m. p. 10°, mixed m. p. with authentic specimen 10° (Found: C, 71·2; H, 6·7; N, 9·7. Calc. for C_8H_9ON: C, 71·1; H, 6·7; N, 9·7%).

Mesidine. The pressure fell to 2620 atm., but the residual gas contained no carbon dioxide. The product, a crystalline solid, was recrystallised from aqueous methanol to give formomesidide (37 g.), m. p. 179°, undepressed on admixture with an authentic specimen (Found: C, 73·5; H, 7·7; N, 8·6. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 8·0; N, 8·6%).

vic-m-*Xylidine.* The pressure fell to 2600 atm. and the residual gas contained carbon dioxide. The product, a crystalline solid, recrystallised from 90% formic acid to give colourless crystals of *4 : 4′-diformamido-3 : 3′ : 5 : 5′-tetramethyldiphenylmethane* (37 g.), m. p. 335—337° (Found: N, 9·0. $C_{19}H_{22}O_2N_2$ requires N, 9·0%). Distillation with soda-lime gave 4 : 4′-diamino-3 : 3′ : 5 : 5′-tetramethyldiphenylmethane, which after crystallisation from methanol had m. p. 124° (Found: C, 80·55; H, 8·6; N, 11·4. Calc. for $C_{17}H_{22}N_2$: C, 80·3; H, 8·65; N, 11·0%). On boiling with 90% formic acid a diformyl derivative identical with that described above was formed. Reaction of the base with acetic anhydride gave the diacetyl derivative, m. p. 305° (Found: C, 74·2; H, 7·7; N, 8·5. Calc. for $C_{21}H_{26}O_2N_2$: C, 74·55; H, 7·7; N, 8·3%). Friedländer and Brand (*Monatsh.*, 1898, **19**, 640) give m. p. 126° for the diamine and m. p. above 280° for the diacetyl derivative.

as-m-*Xylidine.* The pressure fell to 1800 atm. and the residual gas contained 12% of carbon dioxide. Unchanged xylidine was removed by steam-distillation, and the residue which was insoluble in N-hydro-

chloric acid was dissolved in ether. After standing for some days, the crystals which separated were collected and recrystallised from light petroleum (b. p. 100—120°). This gave formo-*as*-*m*-xylidide (18 g.), m. p. 114°, undepressed on admixture with an authentic specimen. The mother-liquors were evaporated, and the dark residue was heated in a sealed tube with concentrated hydrochloric acid (20 c.c.) for 12 hours. The reaction product was cooled, diluted with water, made strongly alkaline with sodium hydroxide, and extracted with ether. The extract was dried (NaOH), the ether removed by distillation, and the residue distilled under reduced pressure. This gave a solid, b. p. 170—200°/1·5 mm., which was crystallised from ethanol to give colourless crystals of 6 : 6′-*diamino*-2 : 2′ : 4 : 4′-*tetramethyldiphenylmethane*, m. p. 122—123° (Found: C, 80·2; H, 8·6; N, 10·9. $C_{17}H_{22}N_2$ requires C, 80·3; H, 8·65; N, 11·0%). Reaction with acetic anhydride gave the *diacetyl* derivative, m. p. 252—253° (Found: C, 74·5; H, 7·6; N, 8·4. $C_{21}H_{26}O_2N_2$ requires C, 74·55; H, 7·7; N, 8·3%).

o-*Toluidine*. The pressure fell to 2500 atm. and the residual gas contained carbon dioxide. The product was steam-distilled to remove traces of unchanged toluidine. The non-volatile residue was a pitch-like solid, completely soluble in 0·1N- but largely insoluble in 3N-hydrochloric acid (Found: C, 80·0; H, 7·8; N, 12·2; NH_2, 13·8%).

p-*Toluidine*. The pressure fell to 2230 atm. and the residual gas contained carbon dioxide. The product, a brown powder, was completely soluble in 0·1N- but largely insoluble in 3N-hydrochloric acid.

Ethyl anthranilate. The residual gas contained carbon dioxide. The product, a dark brown solid, was completely soluble in 0·1N- but largely insoluble in 3N-hydrochloric acid.

p-*Bromoaniline*. The residual gas contained carbon dioxide. The product was a dark solid, undistillable and completely soluble in 0·1N-hydrochloric acid (Found: C, 51·5; H, 3·9; N, 8·6; Br, 31·2%).

m-*Phenylenediamine*. The pressure fell to 2300 atm. and the residual gas contained carbon dioxide. The product, a dark brown powder, was completely soluble in 0·1N- but largely insoluble in 3N-hydrochloric acid (Found: N, 20·4; NH_2, 12·4%).

Benzidine. The product (65 g.) was a purple-black solid, infusible and insoluble in organic solvents but swollen in benzene. It was insoluble in all concentrations of hydrochloric acid, but it absorbed sulphuric and hydrochloric acids from 0·01N-solutions (Found: C, 76·2; H, 6·25; N, 13·95%; acetyl value 350 mg. KOH/g.).

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247. *High-pressure Reactions of Carbon Monoxide. Part II. Reducing Action.*

By G. D. BUCKLEY and N. H. RAY.

Many organic compounds are reduced by carbon monoxide under anhydrous conditions at high temperatures and pressures. In absence of catalyst at 150—250° and 3000 atm., nitro-, nitroso-, and azoxy-benzene are reduced to azobenzene, *N*-phenylhydroxylamine to aniline, and *N*-phenylbenzaldoxime to benzylideneaniline. In presence of Raney cobalt, benzyl alcohol, phenylmethylcarbinol, and benzhydrol are reduced to the corresponding hydrocarbons, benzilic acid gives a mixture of benzophenone and diphenylacetic acid, and benzaldehyde gives a mixture of toluene and benzoic acid. Phenols, ethers, esters, amides, ketones, and purely aliphatic alcohols are not reduced by anhydrous carbon monoxide.

IN the course of work on the reaction of carbon monoxide with arylamines (Part I, preceding paper) evidence was obtained that diarylcarbinols could be reduced to diarylmethanes by the action of carbon monoxide at high temperatures and pressures. Since carbon monoxide can only remove oxygen and cannot supply hydrogen, it seemed likely that novel effects might be achieved by using it as a reducing agent. The effect of carbon monoxide on a range of organic compounds containing typical reducible groups both in presence and in absence of hydrogenation catalysts was therefore investigated.

Nitrobenzene was reduced to azobenzene in high yield at 250° and 3000 atm. with formation of carbon dioxide. Little reduction occurred at 200° or at pressures below 2500 atm., and nickel and cobalt catalysts had no effect on the reaction. It was not found possible to reduce aliphatic nitro-compounds at temperatures below their decomposition points. Nitrosobenzene and azoxybenzene were reduced to azobenzene, *N*-phenylhydroxylamine to aniline, and *N*-phenylbenzaldoxime to benzylideneaniline at lower temperatures, but even in these cases it was essential to maintain a pressure of at least 2500 atm. Although the main product of the reduction of phenylhydroxylamine was aniline, a small amount of azobenzene was also produced. This presumably arose from condensation of aniline with phenylhydroxylamine to give azoxybenzene which then underwent reduction to azobenzene.

Alcohols showed somewhat different behaviour. Benzyl alcohol and benzhydrol underwent little reduction with carbon monoxide at 250° and 3000 atm., but were largely dehydrated to

ethers. However, in presence of Raney cobalt they were reduced to toluene and diphenylmethane, respectively; Raney nickel was somewhat less effective. Phenylmethylcarbinol similarly gave ethylbenzene, and benzilic acid was reduced to diphenylacetic acid accompanied by a considerable quantity of benzophenone. All attempts to reduce purely aliphatic alcohols were unsuccessful, and it was evident that primary aromatic alcohols were reduced much less readily than secondary by carbon monoxide, since benzyl alcohol invariably yielded considerable amounts of dibenzyl ether in addition to toluene, whereas phenylmethylcarbinol gave only the hydrocarbon.

A surprising result was obtained with benzaldehyde. Reaction with carbon monoxide at 250° and 3000 atm. in presence of Raney cobalt gave a mixture of toluene and benzoic acid, and it seems probable that the catalyst induced a Cannizzaro reaction to give benzoic acid and benzyl alcohol, which was then reduced by the carbon monoxide.

Diphenyl ether, dibenzhydryl ether, benzoic acid, ethyl benzoate, acetanilide, benzophenone, benzil, phenol, quinol, β-naphthol, and diacetone alcohol did not react with carbon monoxide in presence or absence of catalysts at 250° and 3000 atm.

Experimental.

(Microanalyses by Dr. A. F. Colson. All m. p.s are uncorrected.)

High-pressure experiments were carried out essentially by the same method and in the same equipment as described in Part I. In no case was there any marked pressure drop during the reaction.

Nitrobenzene. Nitrobenzene (40 g.) was treated with carbon monoxide at 250° and 3000 atm. for 24 hrs. The residual gas contained carbon dioxide. The crude product was distilled with steam; unchanged nitrobenzene (2 g.) distilled over initially, followed by a red solid which was collected, dried, and crystallised from light petroleum (b. p. 100—120°), giving azobenzene (29 g.), m. p. 66—67°, undepressed on admixture with an authentic specimen.

Nitrosobenzene. Nitrosobenzene (10 g.) was treated with carbon monoxide at 150° and 3000 atm. for 18 hrs. The residual gas contained 6·8% of carbon dioxide. The crude tarry product was dissolved in light petroleum (b. p. 100—120°), adsorbed on a column of alumina, and eluted with light petroleum (b. p. 60—80°). Evaporation of the elutriate left azobenzene (7 g.), m. p. 66—67°.

Azoxybenzene. Azoxybenzene (15 g.) was treated with carbon monoxide at 200° and 3000 atm. for 20 hrs. The residual gas contained carbon dioxide. The crude product crystallised from light petroleum (b. p. 100—120°) to give azobenzene (13 g.), m. p. 66—67°.

N-Phenylhydroxylamine. *N*-Phenylhydroxylamine (36 g.) was treated with carbon monoxide at 200° and 3000 atm. for 24 hrs. The residual gas contained carbon dioxide. The crude product was distilled with steam, and the distillate was acidified with hydrochloric acid and extracted with ether. The ethereal extract was evaporated, and the residue crystallised from light petroleum, giving azobenzene (1·25 g.), m. p. 66—67°. The acid solution was treated with excess of sodium hydroxide and extracted with ether, and the extract was dried over sodium hydroxide and distilled. This gave aniline (11·3 g.), b. p. 182°. Reaction with acetic anhydride gave the acetyl derivative, m. p. 117—118°, undepressed on admixture with authentic acetanilide.

N-Phenylbenzaldoxime. *N*-Phenylbenzaldoxime (21 g.) was treated with carbon monoxide at 150° and 3000 atm. for 20 hrs. The residual gas contained carbon dioxide. The product was distilled under reduced pressure, giving benzaldehyde (5·4 g.), b. p. 56—60°/9 mm. (2 : 4-dinitrophenylhydrazone, m. p. 231—232°, undepressed on admixture with an authentic specimen), and benzylideneaniline (12·3 g.), b. p. 150°/9 mm., m. p. 53—54°, undepressed on admixture with an authentic specimen (Found : C, 86·4; H, 5·9; N, 8·0. Calc. for $C_{13}H_{11}N$: C, 86·2; H, 6·1; N, 7·75%).

Benzyl alcohol. Benzyl alcohol (30 g.) and Raney cobalt (0·5 g.) were treated with carbon monoxide at 200° and 3000 atm. for 21 hrs. The residual gas contained carbon dioxide. The product was distilled with steam, and the distillate extracted with ether. The extract was dried (K_2CO_3) and fractionally distilled, giving toluene (10 g.), b. p. 110—111° (dinitro-derivative, m. p. 69—70°, undepressed on admixture with 2 : 4-dinitrotoluene), and unchanged benzyl alcohol (5 g.), b. p. 205—207°. The steam-distillation residue was extracted with ether, and the extract dried (K_2CO_3) and distilled, giving dibenzyl ether (14 g.), b. p. 168—170°/15 mm. (Found : C, 84·7; H, 7·1; *M*, 196. Calc. for $C_{14}H_{14}O$: C, 84·85; H, 7·05%; *M*, 198).

Phenylmethylcarbinol. The carbinol (40 g.) and Raney cobalt (0·5 g.) were treated with carbon monoxide at 250° and 3000 atm. for 24 hrs. The residual gas contained carbon dioxide. The crude product was filtered from catalyst and distilled, giving ethylbenzene (30·7 g.), b. p. 134—136°, $d_4^{20°}$ 0·8670, $n_D^{20°}$ 1·4980 (Found : C, 90·6; H, 9·3. Calc. for C_8H_{10} : C, 90·55; H, 9·45%).

Benzhydrol. Benzhydrol (50 g.) and Raney cobalt (0·5 g.) were treated with carbon monoxide at 200° and 3000 atm. for 20 hrs. The residual gas contained 9·4% of carbon dioxide. The product was filtered from catalyst and fractionally distilled, giving a small amount of unchanged benzhydrol, together with diphenylmethane (23 g.), b. p. 121—122°/9 mm., m. p. and mixed m. p. 23°. There remained a high-boiling residue which was crystallised from light petroleum (b. p. 60—80°), giving *s*-tetraphenylethane (5 g.), m. p. 209°, undepressed on admixture with an authentic specimen.

Benzilic acid. Benzilic acid (30 g.) and Raney cobalt (0·5 g.) were treated with carbon monoxide at 200° and 3000 atm. for 20 hrs. The product was treated with dilute sodium carbonate solution and extracted with ether. Evaporation of the extract gave benzophenone (8·5 g.) (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 236—237°). The sodium carbonate solution was acidified with dilute hydrochloric acid and the precipitate was collected and crystallised from ethanol, giving diphenylacetic

acid (11 g.), m. p. 144—145° (Found : C, 79·5; H, 5·6; equiv., 213. Calc. for $C_{14}H_{12}O_2$: C, 79·25; H, 5·65%; equiv., 212).

Benzaldehyde. Benzaldehyde (40 g.) and Raney cobalt (0·5 g.) were treated with carbon monoxide at 250° and 3000 atm. for 20 hrs. The residual gas contained carbon dioxide. The crude product was washed with an aqueous solution of sodium hydrogen sulphite to remove unchanged aldehyde, and the residual oil was distilled with steam. The distillate contained a colourless oil, which was separated and fractionally distilled to give toluene (9 g.), b. p. 110—112° (2 : 4-dinitro-derivative, m. p. 66°, undepressed on admixture with authentic 2 : 4-dinitrotoluene). The residue from the steam-distillation was extracted with boiling water. On cooling the extract, crystals of benzoic acid (10 g.), m. p. 122°, separated (Found : C, 68·8; H, 4·9; equiv., 124. Calc. for $C_7H_6O_2$: C, 68·5; H, 4·9%; equiv., 122).

IMPERIAL CHEMICAL INDUSTRIES RESEARCH DEPARTMENT,
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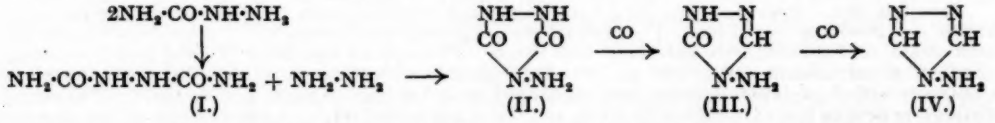
248. *High-pressure Reactions of Carbon Monoxide. Part III. Reaction with Hydrazine.*

By G. D. BUCKLEY and N. H. RAY.

Carbon monoxide reacts with hydrazine under high pressure to give a variety of products depending upon the conditions employed. At 50° and 1000 atm., semicarbazide and ammonia are formed; at 150° and 1000 atm., 4-amino-1 : 2 : 4-triazol-3-one is produced, and at 150° and 3000 atm. the latter is reduced to 4-amino-1 : 2 : 4-triazole.

IN the course of a study of the reactions of carbon monoxide under pressure, that with hydrazine has been investigated (Brit. Pat. Applns. 4720/48, 4721/48). At 150° and 1000 atm. 4-amino-1 : 2 : 4-triazol-3-one (III) was formed, and at 150° and 3000 atm. the main product was 4-amino-1 : 2 : 4-triazole (IV); in both cases ammonium carbonate was formed as a by-product. These were evidently the end products of a complex series of reactions, and in the hope of elucidating the course of the reaction by the isolation of intermediate products, carbon monoxide was caused to react with hydrazine under milder conditions. At temperatures of 20—50° and pressures of 500—1000 atm. the sole products were semicarbazide and ammonia, no carbon dioxide being formed: $CO + 2NH_2{\cdot}NH_2 \longrightarrow NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2 + NH_3$. This was a surprising result. By analogy with the reaction of carbon monoxide and ammonia it might have been expected that the first step would be addition of hydrazine to carbon monoxide to give formylhydrazide, which would then react with itself to give cyclic products; the reduction of hydrazine to ammonia and semicarbazide was quite unforeseen.

The course of the subsequent reactions is fairly clear. Curtius and Heidenreich (*Ber.*, 1894, **27**, 57) have shown that semicarbazide on heating loses hydrazine to give hydrazodicarbonamide (I), which reacts with excess of hydrazine to give 4-aminourazole (II) (Thiele and Stange, *Annalen*, 1894, **283**, 41). Evidently this compound is formed in the course of the reaction of carbon monoxide with hydrazine at 150°, and its enol form must then undergo reduction by the carbon monoxide to give first (III) and then (IV).



This was confirmed by the reduction of 4-aminourazole to 4-amino-1 : 2 : 4-triazol-3-one by carbon monoxide at 150° and 1000 atm. and the reduction of the triazolone to 4-amino-1 : 2 : 4-triazole at 150° and 3000 atm. The most remarkable feature of this series of reactions is the ease with which either the triazole or the triazolone can be produced exclusively by altering the reaction pressure. This emphasises the pressure-dependence of carbon monoxide reductions, previously remarked in Part II (preceding paper).

EXPERIMENTAL.

(Micro-analysis by Dr. A. F. Colson. M. p.s are uncorrected.)

Reaction of Carbon Monoxide with Hydrazine.—(*a*) Hydrazine hydrate (80 c.c., 90%) was charged into a stainless-steel high-pressure autoclave of 300-c.c. capacity, fitted with a magnetically operated reciprocating stirrer. Carbon monoxide was compressed in to about 300 atm., the vessel was heated to 50°, and more gas then added until the pressure reached 500 atm.; after 20 hrs.' stirring at 50° the pressure had fallen to 470 atm. The pressure was released and the residual gas was passed through a scrubber

containing dilute hydrochloric acid; the scrubbed gas contained no carbon dioxide. Evaporation of the acid washings left a crystalline residue, which was identified as ammonium chloride by analysis, by its insolubility in ethanol, by its lack of reducing properties, and by Nessler's test (Found : Cl, 66·3. Calc. for NH_4Cl : Cl, 66·4%).

The aqueous solution remaining in the vessel was filtered and evaporated under reduced pressure at 80°, and the solid residue was crystallised from alcohol, giving semicarbazide (24 g.), m. p. 96°, undepressed on admixture with an authentic specimen (Found : C, 16·2; H, 6·6; N, 55·9. Calc. for CH_5ON_3 : C, 16·0; H, 6·65; N, 56·0%).

(*b*) Hydrazine hydrate (90 c.c., 90%) was stirred with carbon monoxide at 150° and 900—1000 atm. for 20 hrs. The liquid product contained a suspended solid which was collected and found to be ammonium carbonate (5 g.). The filtrate was evaporated to dryness under reduced pressure, and the residue extracted with alcohol. The extract was concentrated to a syrup which eventually crystallised. Recrystallisation from alcohol gave 4-amino-1 : 2 : 4-triazol-3-one (15 g.), m. p. 179—180° (Found : C, 24·0; H, 3·6; N, 55·9. Calc. for $C_3H_4ON_4$: C, 24·0; H, 4·0; N, 56·0%). Curtius and Heidenreich (*Ber.*, 1894, **27**, 2685) give m. p. 181°. Reaction with benzaldehyde gave 4-benzylideneamino-1 : 2 : 4-triazol-3-one, which crystallised from alcohol in leaflets, m. p. 176—177° (Found : C, 57·3; H, 4·1; N, 29·9. Calc. for $C_9H_8ON_4$: C, 57·45; H, 4·25; N, 29·8%). Stollé (*J. pr. Chem.*, 1907, **75**, 423) gives m. p. 178°.

(*c*) Hydrazine hydrate (90 c.c., 90%) was stirred with carbon monoxide at 150° and 3000 atm. for 24 hrs.; the pressure fell to 2410 atm. The crude reaction product was filtered from ammonium carbonate (8·5 g.) and evaporated to dryness under reduced pressure. The syrupy residue was extracted with boiling ethanol (200 c.c.), and the extract was filtered and again evaporated until, on cooling to 0°, the residue crystallised. The product was recrystallised from alcohol–ether (1 : 1) to give 4-amino-1 : 2 : 4-triazole (20 g.), m. p. 80—82°, identical with an authentic specimen (prepared according to *Org. Synth.*, 1944, **24**, 12). 4-Amino-1 : 2 : 4-triazole hydrochloride crystallised from methanol, m. p. 150° (Found : C, 20·0; H, 4·2; N, 46·5; Cl, 29·5. Calc. for $C_2H_3N_4Cl$: C, 19·9; H, 4·15; N, 46·45; Cl, 29·45%). Curtius, Darapsky, and Müller (*Ber.*, 1907, **40**, 835) give m. p. 150°. Reaction with benzaldehyde gave 4-benzylideneamino-1 : 2 : 4-triazole which, crystallised from alcohol, had m. p. 169—170°, undepressed on admixture with an authentic specimen. Ruhemann and Merriman (*J.*, 1905, **87**, 1774) give m. p. 171°.

Reaction of 4-*Aminourazole with Carbon Monoxide.*—4-Aminourazole (2 g.), dissolved in water (5 c.c.), was stirred with carbon monoxide at 150° and 1000 atm. for 20 hrs.; there was no detectable pressure change, but the residual gas contained carbon dioxide. The contents of the vessel were filtered and evaporated to dryness under reduced pressure. The residue was crystallised from alcohol, giving 4-amino-1 : 2 : 4-triazol-3-one (1·0 g.), m. p. 180°, identical with the compound obtained from hydrazine.

Reaction of 4-*Amino*-1 : 2 : 4-*triazol*-3-*one with Carbon Monoxide.*—4-Amino-1 : 2 : 4-triazol-3-one (10 g.) was stirred with carbon monoxide at 15° and 3000 atm. for 15 hrs.; the residual gas contained carbon dioxide. The product was crystallised from alcohol and ether, giving 4-amino-1 : 2 : 4-triazole (7·5 g.), m. p. 80—82°, identical with the product obtained from hydrazine.

The authors are indebted to Mr. F. Bebbington and Mr. E. Wilson for assistance in carrying out the high-pressure experiments described in this and the two preceding papers.

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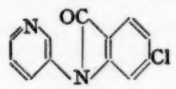
249. *Some Derivatives of* 1 : 5-*Naphthyridine.*

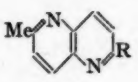
By V. Petrow and B. Sturgeon.

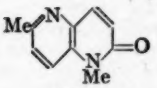
2-Hydroxy-6-methyl-1 : 5-naphthyridine (II; R = OH) has been converted into 2-*chloro*-6-*methyl*-1 : 5-*naphthyridine*, and hence into a number of 2-*substituted* 6-*methyl*-1 : 5-*naphthyridines*. Application of the Doebner–Miller reaction to 5-amino-*N*-methyl-2-pyridone, or methylation of (II; R = OH), gave 2-*keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* (III) which formed a 5-N-*oxide* and a 5-*methiodide*.

The preparation of some derivatives of 1 : 5-naphthyridine was undertaken following the discovery that certain benznaphthyridines (diazaphenanthrenes) synthesised in these laboratories (Petrow, *J.*, 1946, 200, 884, 888) showed outstanding analeptic activity (Thorp, Ph.D. Thesis, London University, 1947, 24). 3-Aminopyridine derivatives formed the starting point of our investigations. Their conversion into 1 : 5-naphthyridines has been described by Bobranski and Sucharda (*Ber.*, 1927, **60**, 1082), who applied the Skraup reaction to 3-aminopyridine, by Adams *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1317), who condensed the same amine with ethyl ethoxymethylenemalonate, and by Rāth, whose work is referred to later. The recent claim of Price and Roberts (*J. Org. Chem.*, 1946, **11**, 463) to have converted 5-chloro-*N*-(3′-pyridyl)anthranilic acid, prepared from 3-aminopyridine and 2 : 4-dichlorobenzoic acid, into 2-chloro-5-aza-acridone must be accepted with caution, for earlier attempts (Kermack and Weatherhead, *J.*, 1942, 726; Petrow, *J.*, 1945, 927) to enforce ring closure of *N*-(3′-pyridyl)anthranilic acid were not successful. The chemical properties of their compound,

and in particular its anomalous reaction with phosphorus oxychloride, would appear to indicate its formulation as the corresponding "anthranil" (I).


(I.)


(II.)


(III.)

Räth (G.P. 507,637) has shown that 5-amino-2-hydroxypyridine hydrochloride undergoes the Skraup and the Doebner–Miller reaction, but the preparation of this intermediate by the published route (G.P. 596,725) is somewhat tedious. We now find that 5-nitro-2-hydroxypyridine is conveniently reduced by the use of reduced iron in acidified water to 5-amino-2-hydroxypyridine, characterised by conversion into both the *mono-* and the *di-benzoyl* derivative. Further, application of the Skraup and the Doebner–Miller reaction to this base has given the corresponding 2-hydroxy-1 : 5-naphthyridine and 2-hydroxy-6-methyl-1 : 5-naphthyridine (II; R = OH) in yields considerably higher than those claimed by Räth. The structure of these compounds is clearly open to question, for ring closure may occur in either the 6- or the 4-position of the pyridine ring. The former alternative was preferred by Räth, and his assumption is supported by the established behaviour of 3-aminopyridine in the Skraup reaction (Bobranski and Sucharda, *loc. cit.*). Numerous attempts on our part rigidly to prove the structure of these compounds have been unsuccessful.

Treatment of (II; R = OH) with phosphorus oxychloride gave 2-*chloro*-6-*methyl*-1 : 5-*naphthyridine* (II; R = Cl), which, by reaction with the appropriate bases, was converted into 2-*anilino*-, 2-p-*chloroanilino*-, 2-*piperidino*-, and 2-*methoxy*-6-*methyl*-1 : 5-*naphthyridine*. The last compound was characterised by conversion into a *mono*-N-*oxide* by McIlwain's method (*J.*, 1943, 324). 2-n-*Butoxy*-6-*methyl*-1 : 5-*naphthyridine* was also prepared as it shows a structural analogy to the tuberculostatic pyridines recently described by Friedman *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 1204). Attempts to obtain the amino-derivative by passage of dry ammonia through a solution of (II; R = Cl) in phenol at 180° failed to give the desired compound, 2-*phenoxy*-6-*methyl*-1 : 5-*naphthyridine* being formed in high yield; also (II; R = Cl) failed to react with N^4-acetylsulphanilamide in nitrobenzene solution in the presence of copper bronze and potassium carbonate.

Application of the Doebner–Miller reaction to 5-amino-*N*-methyl-2-pyridone gave a compound, readily isolated as the *picrate*, to which the structure of a 2-*keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* (III) has been assigned. This constitution is preferred following its synthesis from 2-hydroxy-6-methyl-1 : 5-naphthyridine by methylation with methyl sulphate. The pyridone (III) has been converted into a *monomethiodide* and into a *mono*-N-*oxide*, both of which undoubtedly have the 5-*N*-structures as *N*-methyl-2-pyridones fail to form true quaternary salts (Borsche and Bonacker, *Ber.*, 1921, **54**, 2678). Attempts to convert (III) into 2-chloro-6-methyl-1 : 5-naphthyridine by heating with phosphorus oxychloride gave a black crystalline solid in very low yield. In appearance it resembled a cyanine dye and was probably a compound of this type, for methincyanines are formed by the reaction of a picoline and an *N*-methylpyridone in the presence of phosphorus pentachloride (Moir, *J.*, 1925, **127**, 2338).

Biological examination of the above compounds failed to reveal outstanding activity.

Experimental.

(M. p.s are corrected. Microanalyses by Drs. Weiler and Strauss, Oxford.)

Dibenzoyl Derivative of 5-Amino-2-hydroxypyridine.—A solution of 5-nitro-2-hydroxypyridine (5 g.) (Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1942, **64**, 1696) in water (45 ml.) and concentrated hydrochloric acid (1 ml.) was treated at the boiling point with reduced iron (15 g.) added in portions. When the initial reaction had subsided the mixture was heated under reflux for 1 hour, filtered, and the filtrate and washings taken to dryness under reduced pressure. The red gum so obtained was dissolved in pyridine (40 ml.) and benzoylated by heating with benzoyl chloride (5 g.) for 1 hour at 100°. The *dibenzoyl* derivative of 5-amino-2-hydroxypyridine (3 g.), colourless needles, m. p. 218·5° (Found : C, 71·4; H, 4·9; N, 9·0. $C_{19}H_{14}O_3N_2$ requires C, 71·7; H, 4·4; N, 8·8%), from ethanol–ligroin, separated on addition of water.

5-*Benzamido*-2-*hydroxypyridine.*—The foregoing dibenzoyl derivative (800 mg.), spirit (10 ml.), water (5 ml.), and concentrated hydrochloric acid (10 ml.) were heated under reflux for 30 minutes. The spirit was evaporated, and the product precipitated by the addition of ammonium hydroxide. 5-*Benzamido*-2-*hydroxypyridine* separated from ethanol–light petroleum in colourless needles, m. p. 257° (decomp.) (Found : C, 67·3; H, 4·8; N, 12·8. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·7; N, 13·1%). The compound was readily soluble in dilute potassium hydroxide solution.

2-*Hydroxy*-1 : 5-*naphthyridine.*—A mixture of 5-amino-2-hydroxypyridine [prepared by reduction

of the nitro-compound (20 g.)], dry glycerol (40 g.), arsenic pentoxide (20 g.), and concentrated sulphuric acid (20 ml.) was heated in an oil-bath at 160° for 45 minutes with occasional stirring. The melt was extracted with boiling 2N-hydrochloric acid (200 ml.), and the filtrate concentrated and basified with ammonium hydroxide. 2-Hydroxy-1 : 5-naphthyridine crystallises from aqueous spirit (charcoal) in colourless needles, m. p. 259° (Found : N, 18·7. Calc. for $C_8H_6ON_2$: N, 19·2%); yield 3·3 g. (15%). Răth (*loc. cit.*) records m. p. 258°.

2-*Hydroxy*-6-*methyl*-1 : 5-*naphthyridine* (II; R = OH).—5-Amino-2-hydroxypyridine, prepared by reduction of 10 g. of the nitro-base, was dissolved in concentrated hydrochloric acid (50 ml.), and the solution treated with acetaldehyde (12 g.) whilst cooled in ice. After 1 hour at 0°, the mixture was heated under reflux for 1 hour. The solids precipitated by basification with ammonium hydroxide were extracted with spirit (50 ml.) and water (300 ml.) (charcoal), and the filtrate concentrated, whereupon almost colourless platelets of 2-hydroxy-6-methyl-1 : 5-naphthyridine separated, m. p. 261—262° (Found : N, 17·3. Calc. for $C_9H_8ON_2$: N, 17·5%). The yield (3·2 g., 27%) was not improved by addition of zinc chloride to the reaction mixture. Răth (*loc. cit.*) gives m. p. 260°.

2-*Chloro*-6-*methyl*-1 : 5-*naphthyridine* (II; R = Cl).—The hydroxy-compound (II; R = OH) (1·1 g.) and phosphorus oxychloride (10 ml.) were heated under reflux for 45 minutes. The cooled mixture was poured on ice–ammonium hydroxide, and the precipitated solids collected. 2-*Chloro*-6-*methyl*-1 : 5-*naphthyridine* separated from benzene–ligroin in colourless prisms (1·0 g.), m. p. 181—182° (Found : Cl, 19·6. $C_9H_7N_2Cl$ requires Cl, 19·9%).

2-*Anilino*-6-*methyl*-1 : 5-*naphthyridine* (II; R = NHPh).—The foregoing chloro-compound (1·2 g.) was heated with aniline (15 ml.) under reflux for 2 hours. Dilute sodium hydroxide solution was added, and excess of aniline removed in steam. The residue was recrystallised from benzene–ligroin, giving 2-*anilino*-6-*methyl*-1 : 5-*naphthyridine* (1·5 g.) as pale yellow platelets, m. p. 202—203° (Found : C, 76·6; H, 5·5; N, 17·9. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·5; N, 17·9%).

2-p-*Chloroanilino*-6-*methyl*-1 : 5-*naphthyridine.*—2-Chloro-6-methyl-1 : 5-naphthyridine (1·3 g.), *p*-chloroaniline (2 g.), and nitrobenzene (10 ml.) were heated at the boiling point for 5 minutes and then at 170—180° for 30 minutes. The solids which separated were collected, washed with benzene, and dissolved in alcoholic hydrochloric acid. 2-p-*Chloroanilino*-6-*methyl*-1 : 5-*naphthyridine*, pale yellow plates from aqueous spirit, m. p. 237·5—238° (Found : C, 66·6; H, 4·5; N, 15·3; Cl, 13·7. $C_{15}H_{12}N_3Cl$ requires C, 66·8; H, 4·5; N, 15·6; Cl, 13·2%), separated (66%) on basification with aqueous potassium hydroxide solution.

2-*Piperidino*-6-*methyl*-1 : 5-*naphthyridine.*—The naphthyridine (II; R = Cl) (5 g.) and piperidine (10 ml.) were heated at 175—185° for 7 hours in a sealed tube. Excess of piperidine was removed on the water-bath, and the base liberated with sodium hydroxide and converted into the picrate. 2-*Piperidino*-6-*methyl*-1 : 5-*naphthyridine picrate* (3·8 g. 30%) separated from spirit in silky yellow needles, m. p. 199—199·5° (Found : N, 18·7. $C_{14}H_{17}N_3,C_6H_3O_7N_3$ requires N, 18·4%). The free *base* crystallised from light petroleum (b. p. 40—60°) in pale yellow rhombs, m. p. 62—64° (Found : C, 74·3; H, 7·3; N, 18·5. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%).

2-*Phenoxy*-6-*methyl*-1 : 5-*naphthyridine.*—Dry ammonia was passed through a solution of 2-chloro-6-methyl-1 : 5-naphthyridine (4·5 g.) in phenol (15 g.) at 180° for 7 hours. Dilute sodium hydroxide solution was stirred into the melt, and the solids were collected and washed with water. 2-*Phenoxy*-6-*methyl*-1 : 5-*naphthyridine* was obtained from light petroleum (b. p. 60—80°) in pearly platelets, m. p. 101·5—103·5° (Found : C, 76·1; H, 5·1; N, 11·7. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1; N, 11·9%).

2-*Methoxy*-6-*methyl*-1 : 5-*naphthyridine* (II; R = OMe).—To a boiling solution of sodium (0·3 g.) in absolute methanol (20 ml.), 2-chloro-6-methyl-1 : 5-naphthyridine (1·5 g.) was added, and the mixture heated under reflux for 7 hours. Addition of water, followed by evaporation of the methanol, gave an oil which was isolated with chloroform and purified by two distillations under 20 mm. pressure. 2-*Methoxy*-6-*methyl*-1 : 5-*naphthyridine* was obtained (75%) as a cream-coloured solid, m. p. 53—54° (Found : C, 69·1; H, 5·9; N, 15·8. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·7; N, 16·1%).

2-n-*Butoxy*-6-*methyl*-1 : 5-*naphthyridine*, prepared from (II; R = Cl) and *n*-butanol, formed an ivory-coloured mass, m. p. 37° (Found : C, 72·0; H, 7·8; N, 12·9. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4; N, 13·0%).

2-*Methoxy*-6-*methyl*-1 : 5-*naphthyridine* N-*Oxide.*—The base (2 g.), hydrogen peroxide (2 ml., 100-vol.), and acetic acid (5 ml.) were warmed at *ca.* 70° for 3 hours. Dilution with water precipitated a yellow product which was filtered off, dried, and extracted with boiling light petroleum (b. p. 100—120°). Concentration of the solution deposited thick, colourless rods of 2-*methoxy*-6-*methyl*-1 : 5-*naphthyridine* N-*oxide* (800 mg.), m. p. 154° (Found : C, 63·3; H, 5·2; N, 14·5. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%).

2-*Keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* (III).—(*a*) A solution of 5-nitro-*N*-methyl-2-pyridone (Răth, *Annalen*, 1930, **484**, 57) (10 g.) in spirit (100 ml.) and concentrated hydrochloric acid (0·5 ml.) was treated with reduced iron (30 g.) at the boiling point. After 1 hour under reflux the filtrate and washings were taken to dryness under reduced pressure. The residual amine was dissolved in concentrated hydrochloric acid (50 ml.), and the solution kept overnight with paraldehyde (7·5 g.). It was then heated under reflux for 2 hours, and the product was isolated by basification with ammonia, extracted with chloroform, and finally converted into the picrate. 2-*Keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine picrate* (5·1 g., 30%) separated from spirit (charcoal) in yellow needles, m. p. 189—190° (Found : C, 47·5; H, 3·3; N, 17·1. $C_{10}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 47·6; H, 3·2; N, 17·4%). The *base* formed colourless needles from ligroin, m. p. 136° (Found : C, 68·9; H, 5·9; N, 16·2. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·7; N, 16·1%).

(*b*) 2-Hydroxy-6-methyl-1 : 5-naphthyridine (1·5 g.) was dissolved in aqueous potassium hydroxide solution (0·6 g. in 30 ml. water) by warming, and the solution shaken for 8 hours at room temperature with methyl sulphate (1·3 g.). The solution was acidified with dilute hydrochloric acid, basified with ammonium hydroxide, and the product isolated with chloroform. 2-Keto-1 : 6-dimethyl-1 : 2-dihydro-1 : 5-naphthyridine (Found : C, 68·8; H, 5·9; N, 16·0%) was obtained, identical in m. p. and mixed m. p. with the compound prepared by method (*a*).

2-*Keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* 5-*Methiodide*.—The base (1·2 g.) and methyl iodide (1·1 g.) were heated under reflux for 16 hours in ethanol (15 ml.). Dilution of the warm solution with ether precipitated the crude *methiodide* which was purified by washing with benzene; it crystallised from ethanol in yellow micro-needles (400 mg.), m. p. 213·5—215·5° (decomp.) (Found: I, 40·8. $C_{11}H_{13}ON_2I$ requires I, 40·2%).

2-*Keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* 5-N-*Oxide*.—The pyridone (III) (2 g.), hydrogen peroxide (2·5 ml., 100-vol.) and acetic acid (5 ml.) were warmed at 70°·for 2 hours. Basification with ammonium hydroxide, followed by extraction with chloroform, gave the N-*oxide* (1·1 g.), cream needles from ethanol, m. p. 246·5° (Found: C, 63·5; H, 5·3; N, 14·5. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%).

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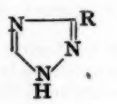
250. *Compounds related to Thiosemicarbazide. Part I. 3-Phenyl-1 : 2 : 4-triazole Derivatives.*

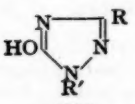
By ERIC HOGGARTH.

The preparation of 3-phenyl-1 : 2 : 4-triazole and two analogues by a novel route which involves the interaction of benzoyl *iso*thiocyanates with hydrazine is described. The constitutions of some of the products of side reactions have been elucidated.

3-PHENYL-1 : 2 : 4-TRIAZOLE (I; R = Ph) was first prepared by Young and Oates (*J.*, 1901, **79**, 659) by heating 5-hydroxy-3-phenyl-1-methyl-1 : 2 : 4-triazole (II; R = Ph, R′ = Me) with phosphorus pentasulphide. The loss of a methyl group in similar reactions had been noted previously by Andreocci (*Atti R. Accad. Lincei*, 1890, **6**, 209). Later Young (*J.*, 1905, **87**, 625) obtained (I; R = Ph) from (II; R = Ph, R′ = H) with phosphorus pentasulphide, and the same compound has been prepared by Pellizzarri (*Gazzetta*, 1911, **41**, 20) by heating benzoylhydrazide (IV; R = Ph) with formamide or formylhydrazide with benzamide. All these reactions gave the product in very unsatisfactory yields. De and Roy Choudhury (*J. Indian Chem. Soc.*, 1928, **5**, 269) claimed that (I; R = Ph) was formed by oxidising benzylidenethiosemicarbazide with hydrogen peroxide, but the m. p. given by them (177°) is not in agreement with that given by Young and Oates (118·5—119°) and now confirmed.

Benzoyl *iso*thiocyanate has been shown to react with phenylhydrazine to give (mainly) 4-benzoyl-1-phenylthiosemicarbazide (Dixon, *J.*, 1889, **55**, 304; Johnson and Menge, *Amer. Chem. J.*, 1904, **32**, 358). We have found, however, that if the *iso*thiocyanate was dropped into an excess of hydrazine, a mixture of 3-*phenyl*-1 : 2 : 4-*triazole*-5-*thiol* (III; R = Ph) and benzoyl hydrazide (IV; R = Ph) was formed. It may be presumed that 4-benzoylthiosemicarbazide is formed first and then spontaneously cyclises with loss of water. If only one molecular proportion of hydrazine was used, side reactions took place and instead of the previously clear reaction liquid, a voluminous precipitate was formed. This precipitate consisted of 1 : 4-dibenzoylthiosemicarbazide (V; R = Ph), and the *salt* of this compound with hydrazine. The salt could be converted into (V; R = Ph) by treatment with mineral acid, and was prepared from an alcoholic solution of its constituent parts.


(I.)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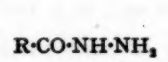
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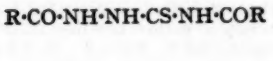
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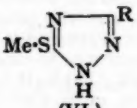
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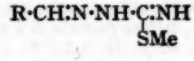
(VII.)

p-*Methoxybenzoyl* and p-*chlorobenzoyl* iso*thiocyanates* were prepared by the method of Johnson and Chernoff (*J. Amer. Chem. Soc.*, 1912, **34**, 167). The *p*-methoxybenzoyl compound, a very low-melting solid, was added molten to excess of hydrazine hydrate in alcohol and gave the *thiol* (III; R = *p*-MeO·C_6H_4) and *p*-methoxybenzoylhydrazide (IV; R = *p*-MeO·C_6H_4). The

yields of purified thiol in this case (averaging 37% in 3 runs) were always higher than in the reaction with benzoyl *iso*thiocyanate (23% in 3 runs). 1 : 4-*Di*-p-*methoxybenzoylthiosemicarbazide* (V; R = *p*-MeO·C_6H_4) was formed as a by-product when only 1 molecular proportion of hydrazine hydrate was taken, but a salt of the latter compound with hydrazine, though apparently formed, could not be crystallised. *p*-Chlorobenzoyl *iso*thiocyanate (dissolved in a little ether) reacted with excess of hydrazine to give the *thiol* (III; R = *p*-ClC_6H_4) and *p*-chlorobenzoylhydrazide (IV; R = *p*-ClC_6H_4). The yield of the thiol was again higher than with benzoyl *iso*thiocyanate (36% in 3 runs). When powdered *p*-chlorobenzoyl *iso*thiocyanate was used instead of an ethereal solution, a considerable amount of 1 : 4-*di*-p-*chlorobenzoylthiosemicarbazide* (V; R = *p*-ClC_6H_4) was formed, even in the presence of an excess of hydrazine.

The thiols (III; R = Ph, *p*-MeO·C_6H_4, or *p*-ClC_6H_4) were smoothly converted into the phenyltriazoles (I; R = Ph, *p*-MeO·C_6H_4, or *p*-ClC_6H_4) by boiling in alcohol with Raney nickel catalyst. Compound (III; R = Ph) was also " desulphurised " by treatment with hydrogen peroxide. Confirmation of the assigned structures was obtained by methylation of two of the thiols to give the corresponding 5-methylthio-compounds (VI; R = Ph or *p*-MeO·C_6H_4) identical with those prepared by oxidation with ferric chloride of the corresponding 1-benzylidene-*S*-methyl*iso*thiosemicarbazides (VII; R = Ph or *p*-MeO·C_6H_4). 5-Methylthio-3-phenyl-1 : 2 : 4-triazole has been obtained by the latter route by De and Chakravarti (*J. Indian Chem. Soc.*, 1930, **7**, 875) using hydrogen peroxide as oxidising agent. Attempts have been made to prepare 5-amino-3-phenyl-1 : 2 : 4-triazole derivatives from the 5-methylthio-compounds on analogy with well-known reactions in the pyrimidine series, but no reaction could be detected between (VI; R = Ph) or the corresponding *sulphone* with ammonia or 2-diethylaminoethylamine.

Experimental.

3-Phenyl-1 : 2 : 4-triazole-5-thiol (III; R = Ph).—Hydrazine hydrate (70 c.c. containing 19·0 g. of hydrazine, by titration) and alcohol (130 c.c.) were stirred, with cooling by an ice-bath, whilst benzoyl *iso*thiocyanate (33 g.) was run in during 5 minutes. The temperature rose to 55°, and stirring at room temperature was continued overnight. The clear, pale yellow liquid was evaporated under reduced pressure, the residue diluted with water (200 c.c.), made strongly acid (hydrochloric acid), and the precipitate collected. This precipitate was ground in a mortar with N-hydrochloric acid (100 c.c.), and the solid again collected, washed well with water, and dried. The crude *thiol* (9·5 g., m. p. 240—245°) was crystallised from water (1 l.) with charcoal, giving colourless flat needles (8·1 g.), m. p. 256° (Found : C, 54·3; H, 4·0; N, 23·6; S, 17·7. $C_8H_7N_3S$ requires C, 54·2; H, 4·0; N, 23·7; S, 18·1%). The acid extracts were exactly neutralised with sodium hydroxide solution and evaporated under reduced pressure, and the residue was extracted with chloroform. The solvent was evaporated from the dried extracts, leaving a colourless crystalline mass of benzoylhydrazide (18·5 g., m. p. 100—104°), which crystallised from benzene in large colourless prisms (12·6 g.), m. p. 112° not depressed by admixture with an authentic specimen, prepared as described by Curtius and Struve (*J. pr. Chem.*, 1894, **50**, 295) (Found : C, 62·2; H, 5·8; N, 20·8. Calc. for $C_7H_8ON_2$: C, 61·8; H, 5·9; N, 20·6%).

When the above reaction was carried out with only 30 c.c. of the hydrazine hydrate solution, a precipitate was formed which was collected and washed with 50% aqueous alcohol. The filtrates were evaporated and separated into 3-phenyl-1 : 2 : 4-triazole-5-thiol (1·9 g., m. p. 254°) and benzoylhydrazide (5·5 g., m. p. 113°) as previously. The precipitate (7·5 g., m. p. 140—145°) was crystallised from alcohol (400 c.c.), giving the *hydrazine* salt of 1 : 4-dibenzoylthiosemicarbazide as colourless, flat, shining needles (1·1 g.), m. p. 157° (Found : C, 54·6, 54·5; H, 5·0, 4·75; N, 21·4; S, 9·6. $C_{15}H_{13}O_2N_3S,N_2H_4$ requires C, 54·4; H, 5·1; N, 21·2; S, 9·7%). The mother-liquor was concentrated, filtered from flocculent material (charcoal), and allowed to crystallise, giving 1 : 4-dibenzoylthiosemicarbazide as colourless, square plates (0·75 g.), m. p. 174° (Found : C, 59·8; H, 4·0; N, 14·5; S, 10·7. Calc. for $C_{15}H_{13}O_2N_3S$: C, 60·2; H, 4·35; N, 14·1; S, 10·7%). The hydrazine salt (0·5 g.) was dissolved in hot alcohol, treated with N-hydrochloric acid (10 c.c.), diluted with water, and the precipitated 1 : 4-dibenzoylthiosemicarbazide (0·35 g., m. p. 172°) crystallised from alcohol, giving colourless, square plates (0·25 g.), m. p. 173° (Found : C, 59·9; H, 3·9; N, 13·9%). A specimen of 1 : 4-dibenzoylthiosemicarbazide prepared by Fehrenbach and Stolle's method (*J. pr. Chem.*, 1929, **122**, 289) had m. p. 173° not depressed by admixture with the compound isolated in either of the above ways. The salt was formed by dissolving the dibenzoyl compound (0·5 g.) in alcohol, adding 50% hydrazine hydrate (1 c.c.) and allowing it to crystallise. Faintly yellow needles (0·25 g.), m. p. 156°, separated and were crystallised from alcohol, giving the salt, m. p. 157° not depressed by admixture with the compound isolated from the original reaction (Found : C, 54·3; H, 5·2; N, 21·2%). Care must be taken not to boil the alcoholic solutions of the salt or rapid decomposition with evolution of hydrogen sulphide takes place.

p-*Methoxybenzoyl* iso*Thiocyanate*.—*p*-Methoxybenzoyl chloride (51 g.) and lead thiocyanate (107 g.) were boiled with benzene (200 c.c.) (oil-bath) with good stirring for 1 hour, filtered, and the benzene removed under reduced pressure. The residue was distilled, giving a pale yellow oil, b. p. 133—135°/2·0 mm., which was redistilled (43 g.), b. p. 116—118°/0·3 mm., and then solidified to a crystalline mass of the iso*thiocyanate*, m. p. 28—30° (Found : N, 7·2; S, 16·3. $C_9H_7O_2NS$ requires N, 7·25; S, 16·6%).

3-p-Methoxyphenyl-1 : 2 : 4-triazole-5-thiol (III; R = *p*-MeO·C_6H_4).—Hydrazine hydrate (35 c.c.) in alcohol (70 c.c.) was treated with *p*-methoxybenzoyl *iso*thiocyanate (19·3 g.), added molten from a warm tap-funnel during 5 minutes, and gave crude *thiol* (12·8 g., m. p. 240—242°) and *p*-methoxybenzoylhydr-

azide (6·0 g., m. p. 110°), separated as previously. The thiol was crystallised from alcohol (200 c.c.) and water (250 c.c.), giving large, faintly coloured needles (9·1 g.), m. p. 257° (Found : C, 51·7; H, 4·4; S, 15·4. $C_9H_9ON_3S$ requires C, 52·2; H, 4·35; S, 15·5%). The hydrazide was crystallised from xylene, giving colourless plates (2·4 g.), m. p. 133° not depressed by admixture with a sample of *p*-methoxybenzoylhydrazide prepared as described by Curtius and Melsbach (*J. pr. Chem.*, 1910, **81**, 501) (Found : C, 57·8; H, 5·8; N, 16·8. Calc. for $C_8H_{10}O_2N_2$: C, 57·8; H, 6·0; N, 16·9%). When only 15 c.c. of hydrazine hydrate were used in the above experiment, a precipitate separated; this was collected, and boiled with alcohol (200 c.c.) and concentrated hydrochloric acid (5 c.c.). Water was added, and the solid collected, and crystallised from 2-ethoxyethanol (much insoluble material), giving 1 : 4-*di*-p-*methoxybenzoylthiosemicarbazide* as colourless needles (0·25 g.), m. p. 210° not depressed by admixture with this compound prepared as below (Found : C, 56·5; H, 4·8; N, 12·0; S, 9·3. $C_{17}H_{17}O_4N_3S$ requires C, 56·8; H, 4·7; N, 11·7; S, 8·9%). The filtrate from the main part of the experiment gave the thiol (7·1 g.), m. p. 256°, and *p*-methoxybenzoylhydrazide (2·4 g.), m. p. 133°.

1 : 4-*Di*-p-*methoxybenzoylthiosemicarbazide* (V; R = *p*-MeO·C_6H_4).—*p*-Methoxybenzoylhydrazide (1·7 g.) was dissolved in warm alcohol (100 c.c.) and stirred whilst *p*-methoxybenzoyl *iso*thiocyanate (1·9 g.) was added during 5 minutes. The solid was collected after 1 hour, washed with water, and crystallised from 2-ethoxyethanol, giving colourless needles (2·8 g.), m. p. 210° (Found : C, 56·8; H, 4·6; S, 8·7%).

p-*Chlorophenyl* iso*Thiocyanate*.—This *compound* (prepared as described for the *p*-methoxybenzoyl analogue) was distilled, giving a pale yellow oil, b. p. 130—133°/2·0 mm., which solidified to a yellow crystalline mass, m. p. 48° (Found : N, 7·0; S, 15·9. C_8H_4ONClS requires N, 7·1; S, 16·2%).

3-p-*Chlorophenyl*-1 : 2 : 4-*triazole*-5-*thiol* (III; R = *p*-C_6H_4Cl).—Hydrazine hydrate (35 c.c.), alcohol (70 c.c.), and a solution of *p*-chlorobenzoyl *iso*thiocyanate (19·8 g.) in ether (60 c.c.) gave, as previously, the crude *thiol* (10 g.), m. p. 288°, and *p*-chlorobenzoylhydrazide (7·8 g.), m. p. 150°. The thiol was crystallised from aqueous alcohol, giving a white microcrystalline powder (8·5 g.), m. p. 296—297° (Found : C, 45·4; H, 2·4; N, 19·8; S, 14·8. $C_8H_6N_3ClS$ requires C, 45·4; H, 2·8; N, 19·9; S, 15·1%). The hydrazide crystallised from water in shining leaflets (6·2 g.), m. p. 164°, identical with the compound prepared by Kahl's method (*Centr.*, 1904, II, 1493) (Found : C, 49·6; H, 4·1; N, 16·6. Calc. for $C_7H_7ON_3Cl$: C, 49·3; H, 4·1; N, 16·4%). When the powdered *iso*thiocyanate (9·8 g.) was added to a rapidly stirred mixture of hydrazine hydrate (18 c.c.) and alcohol (35 c.c.), a thick precipitate was formed which after being stirred overnight, was collected, washed with alcohol, and crystallised from 2-ethoxyethanol, giving colourless needles of 1 : 4-*di*-p-*chlorobenzoylthiosemicarbazide* (0·85 g.), m. p. 235° (decomp.) (Found : C, 48·8; H, 3·0; S, 9·0. $C_{15}H_{11}O_2N_3Cl_2S$ requires C, 48·9; H, 3·0; S, 8·7%). The filtrates gave 3-*p*-chlorophenyl-1 : 2 : 4-triazole-5-thiol (1·1 g.), m. p. 292—293° (Found : S, 15·3%), and *p*-chlorophenylhydrazide (4·4 g.), m. p. 164° (Found : N, 16·7%).

1 : 4-*Di*-p-*chlorobenzoylthiosemicarbazide* (V; R = *p*-C_6H_4Cl).—*p*-Chlorobenzoyl *iso*thiocyanate (2·0 g.) and *p*-chlorobenzoylhydrazide (1·7 g.) gave the dibenzoyl compound (3·0 g.), m. p. 234° (decomp.), identical with this compound as isolated in the previous experiment (Found : C, 49·1; H, 2·9; S, 8·7%).

3-*Phenyl*-1 : 2 : 4-*triazole* (I; R = Ph).—(*a*) 3-Phenyl-1 : 2 : 4-triazole-5-thiol (1·8 g.) was boiled with Raney nickel catalyst (*ca.* 3·0 g.) in alcohol (20 c.c.) for 3 hours, filtered, and the filtrate evaporated, giving a colourless syrup which, on being scratched, solidified to a crystalline mass (1·4 g.), m. p. 110°. This crude material was free from sulphur and crystallised from light petroleum (b. p. 100—120°), giving 3-phenyl-1 : 2 : 4-triazole, which formed colourless needles (1·1 g.), m. p. 121° (Found : C, 66·1; H, 4·9; N, 28·6. Calc. for $C_8H_7N_3$: C, 66·2; H, 4·8; N, 29·0%).

(*b*) The same thiol (1·8 g.) was boiled in acetic acid (25 c.c.), and " perhydrol " (5 c.c.) added. When the vigorous reaction subsided, the acetic acid was evaporated under reduced pressure, the residue neutralised (sodium carbonate solution), the triazole extracted with ether, the extract dried (Na_2SO_4), and the solvent evaporated. The residue (1·3 g., m. p. 118°) was free from sulphur, and crystallised from light petroleum (b. p. 100—120°) in colourless needles (1·0 g.), m. p. 121° (Found : C, 65·9; H, 4·5%).

3-p-*Methoxyphenyl*-1 : 2 : 4-*triazole* (I; R = *p*-MeO·C_6H_4).—The thiol (2·1 g.) and Raney nickel catalyst (3·0 g.) in alcohol (25 c.c.) gave the *triazole*, which crystallised from methyl alcohol (small volume) giving large masses of colourless prisms (1·0 g.), m. p. 186° (Found : C, 61·5; H, 5·4; N, 23·7. $C_9H_9ON_3$ requires C, 61·7; H, 5·1; N, 24·0%).

3-p-*Chlorophenyl*-1 : 2 : 4-*triazole* (I; R = *p*-ClC_6H_4).—The thiol (1·05 g.) and Raney nickel catalyst gave the *triazole*, which crystallised from xylene in clumps of needles (0·5 g.), m. p. 182° (Found : C, 53·5; H, 3·2; N, 23·5. $C_8H_6N_3Cl$ requires C, 53·5; H, 3·3; N, 23·4%).

1-*Benzylidene*-S-*methyliso*thiosemicarbazide (VII; R = Ph).—A mixture of the hydriodide of *S*-methyl*iso*thiosemicarbazide (11·5 g.) in water (5 c.c.) and benzaldehyde (5·5 g.) in alcohol (15 c.c.) was heated at 70—80° for 6 hours. Water (200 c.c.) was added, the alcohol removed under reduced pressure, and the hot solution filtered (charcoal) and allowed to crystallise. The resulting *hydriodide* (11·1 g., m. p. 78—82°) was crystallised from water, giving pale yellow needles (8·0 g.), m. p. 134° (after drying in a vacuum; sinters at 98°)(Found : C, 33·4; H, 3·7. $C_9H_{11}N_3S,HI$ requires C, 33·65; H, 3·7%). This salt (6·5 g.) was rubbed with warm 10% sodium carbonate solution until the liberated oil solidified, the solid collected, dissolved in boiling light petroleum (b. p. 60—80°, 250 c.c.), anhydrous potassium carbonate added, and the filtered solution allowed to crystallise, giving colourless prisms of the *base* (3·1 g.), m. p. 82° (Found : C, 55·7; H, 5·4; S, 16·8. $C_9H_{11}N_3S$ requires C, 55·95; H, 5·7; S, 16·6%). De and Chakravorty (*loc. cit.*) state that they were unable to crystallise this compound. No difficulty was experienced if the hydriodide was first purified.

1-p-*Methoxybenzylidene*-S-*methyliso*thiosemicarbazide (VII; R = *p*-MeO·C_6H_4).—The hydriodide of *S*-methyl*iso*thiosemicarbazide (5·8 g.) and *p*-methoxybenzaldehyde (3·6 g.) gave a *hydriodide* (7·6 g.), m. p. 178° (sinters at 110°) (Found : C, 33·7; H, 3·6; N, 12·1. $C_{10}H_{13}ON_3S,HI$ requires C, 34·2; H, 4·0; N, 12·0%). The *thiosemicarbazide* (isolated as previously) crystallised from benzene–light petroleum (b. p. 60—80°), giving colourless needles (2·9 g.), m. p. 97° (Found : C, 53·9; H, 6·0; S, 14·0. $C_{10}H_{13}ON_3S$ requires C, 53·8; H, 5·8; S, 14·35%)

5-Methylthio-3-phenyl-1 : 2 : 4-triazole (VI; R = Ph).—(*a*) 3-Phenyl-1 : 2 : 4-triazole-5-thiol (1·8 g.) in alcohol (10 c.c.) was heated to 60°, treated with a solution of methyl iodide (1·5 g.) in alcohol (5 c.c.) in a closed vessel, set aside overnight, heated under reflux for 3 hours, and then evaporated under reduced pressure. The residue was rubbed with N-sodium hydroxide solution until it was almost all in solution, filtered (charcoal), and the filtrate exactly neutralised with N-hydrochloric acid. The precipitate (1·6 g., m. p. 160°) was crystallised from a small volume of 50% aqueous alcohol, giving the methylthio-compound as colourless leaflets (0·9 g.), m. p. 161° (Found: C, 56·5; H, 4·4; S, 16·8. Calc. for $C_9H_9N_3S$: C, 56·5; H, 4·7; S, 16·75%). De and Chakravorty (*loc. cit.*) give m. p. 164°. This compound was recovered unchanged after 6 hours' heating with 2-diethylaminoethylamine at 170—175°.

(*b*) 1-Benzylidene-*S*-methyl*iso*thiosemicarbazide (1·9 g.) in a mixture of acetic acid (25 c.c.) and water (25 c.c.) was stirred at 90° whilst a solution of ferric chloride (anhydrous, 3·5 g.) in water (10 c.c.) was added during 10 minutes. Stirring was continued at 90° until the reddish colour was discharged (0·5 hour), the solution evaporated under reduced pressure, and ether (100 c.c.) added, followed by an excess of 20% potassium hydrogen carbonate solution. After thorough shaking, the ether was poured off, the residue extracted with several small amounts of ether, and the solvent evaporated from the combined extracts. The residual solid (1·3 g., m. p. 156°) was crystallised first from aqueous alcohol and then from benzene, giving colourless flat needles (1·0 g.), m. p. 161° not depressed by the compound as prepared under (*a*) (Found: C, 57·0; H, 4·9; S, 16·6%).

5-Methylthio-3-p-methoxyphenyl-1 : 2 : 4-triazole (VI; R = *p*-MeO·C_6H_4).—(*a*) The thiol (1·1 g.) and methyl iodide (0·8 g.) in alcohol (50 c.c.) gave the *methylthio*-derivative, which crystallised from benzene containing a little light petroleum (b. p. 60—80°) in colourless leaflets or flat needles (0·8 g.), m. p. 126° (Found: C, 54·1; H, 4·7; N, 18·7; S, 14·9. $C_{10}H_{11}ON_3S$ requires C, 54·3; H, 5·0; N, 19·0; S, 14·5%).

(*b*) Oxidation of 1-*p*-methoxybenzylidene-*S*-methyl*iso*thiosemicarbazide (1·5 g.) in acetic acid (20 c.c.) and water (20 c.c.) by a solution of ferric chloride (anhydrous, 2·5 g.) in water (10 c.c.) as described for the benzylidene compound gave the methylthiotriazole (0·9 g., m. p. 120—122°), which crystallised from benzene–light petroleum (b. p. 60—80°) in colourless flat needles (0·75 g.), m. p. 126° not depressed by admixture with the compound prepared as in (*a*) (Found: C, 54·0; H, 4·8; S, 14·5%).

5-Methylsulphonyl-3-phenyl-1 : 2 : 4-triazole.—The methylthio-compound (1·9 g.) in acetic acid (30 c.c.) was treated at 25—30° with a solution of potassium permanganate (3·2 g.) in water (30 c.c.) added during 0·25 hour. The manganese dioxide was coagulated by warming on the steam-bath and filtered off, and the residue washed with 10% acetic acid. The filtrates were evaporated under reduced pressure, the residue made neutral with potassium hydrogen carbonate, and the precipitate extracted with chloroform. Evaporation of the solvent gave a colourless crystalline mass which crystallised from water or xylene in large colourless needles (1·0 g.), m. p. 160° (Found: C, 48·7; H, 4·1; S, 14·3. $C_9H_9O_2N_3S$ requires C, 48·5; H, 4·0; S, 14·4%). This *sulphone* was recovered unchanged after 15 hours' heating at 120° with alcoholic ammonia or after 6 hours at 160—170° with 2-diethylaminoethylamine.

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251. *Compounds related to Thiosemicarbazide. Part II.* 1-*Benzoylthiosemicarbazides.*

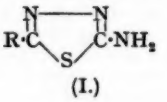
By ERIC HOGGARTH.

Preparations of 1-benzoylthiosemicarbazides are described, and the constitution of these compounds established by dehydration experiments with a variety of reagents. Evidence is adduced to show that, after initial substitution at position 1, thiosemicarbazide is attacked by benzoyl chlorides in pyridine at both positions 2 and 4. A convenient preparation of 3-phenyl-1 : 2 : 4-triazole-5-thiols (Part I) is afforded by dehydration of 1-benzoylthiosemicarbazides under alkaline conditions.

1-BENZOYL derivatives of 4-aryl- and 4-alkyl-thiosemicarbazides have been prepared by reaction of benzoylhydrazide with aryl and alkyl *iso*thiocyanates (Marckwald and Bott, *Ber.*, 1896, **29**, 2914; Oates and Young, *J.*, 1901, **79**, 659). Both Fehrenbach and Stolle (*J. pr. Chem.*, 1929, **122**, 289) and De (*J. Indian Chem. Soc.*, 1930, **7**, 651) mention 1-benzoylthiosemicarbazide itself, but neither describe its preparation nor characterise it. Fromm (*Annalen*, 1926, **447**, 259) reported that attempts to benzoylate thiosemicarbazide directly in pyridine or under the Schotten–Baumann conditions resulted in simultaneous elimination of water to give a cyclised product. The inference that 1-benzoylthiosemicarbazides not carrying alkyl or aryl groups are, like the corresponding unsubstituted 4-benzoylthiosemicarbazides (Part I), unstable, has proved to be incorrect.

1-*Benzoylthiosemicarbazide* (II; R = Ph) has been prepared (*a*) by reaction of benzoylhydrazide with ammonium thiocyanate, (*b*) by cautiously heating thiosemicarbazide with the theoretical amount of benzoyl chloride, and (*c*) by benzoylation in ice-cold pyridine. The last route is by far the most convenient but gives in addition to the main product a small quantity of 1 : 4-dibenzoylthiosemicarbazide. 1-p-*Chlorobenzoyl-*, 1-p-*methoxybenzoyl-* and 1-p-*nitrobenzoylthiosemicarbazides* were also prepared by the latter route, as were the 1-benzoyl and 1-p-*methoxy-*

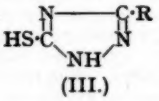
benzoyl derivatives of 4-phenyl-, 4-methyl-, 2 : 4-*dimethyl*-, and 4 : 4-*dimethyl*-thiosemicarbazides. The 4-phenyl- and 4-methyl-thiosemicarbazide derivatives were identical with the compounds obtained by the method of Marckwald and Bott (*loc. cit.*). Primarily, these compounds were prepared in order to study their dehydration reactions, and such studies have established that the benzoyl group is, as expected, in position 1. All dehydrations with the *acidic* reagents described here gave as one of the products (and often as the only product) a 2-amino-5-aryl-1 : 3 : 4-thiadiazole (I). Such sompounds could only arise from 1-benzoylthiosemicarbazides (II) which could (theoretically) give, in addition, 3-aryl-1 : 2 : 4-triazole-5-thiols (III). On the other hand, 4-benzoylthiosemicarbazides (IV) can give rise to (only) the triazoles (III).



(I.)

$R{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CS{\cdot}NH_2$

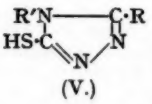
(II.)



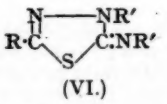
(III.)

$H_2N{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}COR$

(IV.)



(V.)



(VI.)

1-Benzoyl-, 1-*p*-methoxybenzoyl-, and 1-*p*-nitrobenzoyl-thiosemicarbazide were dehydrated by phosphoric acid to give thiadiazoles (I; R = Ph, *p*-MeO·C_6H_4, or *p*-ClC_6H_4) and no triazole was detected. From the *p*-methoxybenzoyl compound, *p*-methoxybenzoic acid, arising presumably by simultaneous hydrolysis, was also found. The results were similar with 1-benzoyl-, 1-*p*-methoxybenzoyl-4-methyl-, -2 : 4-dimethyl-, and -4 : 4-dimethyl-thiosemicarbazide. Similar reactions were effected with sulphuric acid, but from the methoxybenzoyl compounds the product was water-soluble, owing apparently to sulphonation. The constitutions of the thiadiazoles follow from their basic properties and stability towards desulphurisation by hydrogen peroxide and Raney nickel catalyst. Under these conditions the sulphur atom of the triazole-thiols is removed (Part I). In a number of cases the thiadiazoles were also synthesised for comparison by a route used by Young and Eyre (*J.*, 1901, **79**, 54) for 2-amino-5-phenyl-1 : 3 : 4-thiadiazole. Fromm (*loc. cit.*) considered that the compound described by Young and Eyre as 2-amino-5-phenyl-1 : 3 : 4-thiadiazole was really 3-phenyl-1 : 2 : 4-triazole-5-thiol, his main reason being the failure of the compound to show the usual reaction of a primary amine with an *iso*thiocyanate. This conclusion must be regarded as erroneous. The dehydration of 1-benzoyl-4-phenylthiosemicarbazide with phosphoric acid differed from all preceding cases in that both aminothiadiazole and triazole-thiol were formed. 1 : 4-Dibenzoylthiosemicarbazide gave 2-benzamido-5-phenyl-1 : 3 : 4-thiadiazole only.

Marckwald and Bott (*loc. cit.*) reported that when 1-benzoyl-4-phenylthiosemicarbazide was dehydrated with acetyl chloride the product was 2-phenylamino-5-phenyl-1 : 3 : 4-thiadiazole, whilst with benzoyl chloride as dehydrating agent they obtained 3 : 4-diphenyl-4 : 1 : 2-triazole-5-thiol (V; R = R′ = Ph). Reinvestigation has shown that, in fact, both give a mixture of thiadiazole and triazole, although the predominating isomer in each instance is that isolated by the earlier authors. Application of benzoyl and acetyl chlorides to the dehydration of other 1-benzoylthiosemicarbazides has given results which, allowing for simultaneous acetylation or benzoylation, do not differ greatly from those recorded for phosphoric acid. Dehydration of 1-benzoyl-4-methylthiosemicarbazide with benzoyl chloride gave a small amount of 3-phenyl-4-methyl-4 : 1 : 2-triazole-5-thiol (V; R = Ph, R′ = Me) which could not be detected amongst the products of dehydration by other reagents. In the main, however, the products of such acidic cyclisations are determined by the substituents of the benzoylthiosemicarbazide molecule and are only to a small degree affected by the reagent used for dehydration.

In marked contrast to the foregoing, if 1-benzoylthiosemicarbazides are boiled with an alcoholic solution of sodium ethoxide, piperidine, or other strong base the elimination of water which takes place under such *alkaline* conditions occurs with exclusive formation of the triazole-thiols (III). In the representative examples studied, the yield of thiol approached the theoretical, and this is the most satisfactory method of preparing these compounds.

The isolation of a small amount of 1 : 4-dibenzoylthiosemicarbazide from the reaction of benzoyl chloride with thiosemicarbazide in pyridine suggested that the dibenzoyl compound might be most conveniently prepared by reaction of 1-benzoylthiosemicarbazide with benzoyl chloride under the same conditions. 1 : 4-Dibenzoylthiosemicarbazide was isolated, but there was also formed much 1 : 2-dibenzoylhydrazine. This seems to indicate that benzoyl chloride attacks position 2 of 1-benzoylthiosemicarbazide as well as position 4, and that 1 : 2-dibenzoyl-

thiosemicarbazide is decomposed, probably during isolation. 1 : 2-Di-*p*-chlorobenzoyl- and 1 : 2-di-*p*-nitrobenzoyl-hydrazine were isolated as by-products in the preparation of the corresponding 1-benzoylthiosemicarbazides and presumably arise in the same way. Corresponding by-products were not found in the other benzoylation reactions, but as those dibenzoylhydrazines detected are very insoluble and were isolated only in small amounts, failure may be due simply to different relative solubilities.

Experimental.

1-*Benzoylthiosemicarbazide* (II; R = Ph).—(*a*) Benzoylhydrazide (6·8 g.) was dissolved in alcoholic hydrogen chloride solution (50 c.c.) and evaporated under reduced pressure, the residue dried by evaporation of several small amounts of alcohol and heated under reflux for 18 hours with a solution of dry ammonium thiocyanate (4·0 g.) in alcohol (200 c.c.). Ammonium chloride was filtered off, the solvent removed under reduced pressure, and the residue crystallised several times from water, giving colourless leaflets (1·1 g.), m. p. 196° (decomp.) (Found : S, 16·3. $C_8H_9ON_3S$ requires S, 16·4%), of the *thiosemicarbazide*.

(*b*) Finely powdered thiosemicarbazide (9·1 g.) and benzoyl chloride (14 g.) were mixed ice-cold and cautiously warmed. When the vigorous reaction subsided, the solid was broken up, boiled with alcohol (100 c.c.), filtered hot from a small amount of insoluble material, and allowed to crystallise. The solid which separated was crystallised several times from water, giving colourless leaflets (0·95 g.), m. p. 198° (decomp.) (Found : C, 49·7; H, 4·5. $C_8H_9ON_3S$ requires C, 49·3; H, 4·6%). The material insoluble in water crystallised from alcohol in colourless square plates (0·3 g.), m. p. 223°, identical with 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (see later). A further quantity of 1-benzoylthiosemicarbazide was obtained by diluting the original alcoholic mother-liquor with light petroleum (b. p. 60—80°) and crystallising the precipitate several times from water, giving colourless leaflets (1·7 g.), m. p. 194—196° (decomp.) (Found : C, 49·1; H, 4·4%).

(*c*) Powdered thiosemicarbazide (9·1 g.) was suspended in dry pyridine (100 c.c.) cooled to −5°, and benzoyl chloride (14·0 g.) added dropwise below 0° (0·5 hour). After 12 hours' stirring during which room temperature was attained, water (500 c.c.) was added, the pyridine removed under reduced pressure, and the oily precipitate rubbed until hard, collected, and added to boiling water (300 c.c.). The liquid was filtered (charcoal) and allowed to cool, giving colourless leaflets (12·1 g.), m. p. 196—198° (decomp.). The oily material insoluble in water was crystallised twice from alcohol, giving flat needles (0·5 g.), m. p. 174° not depressed by admixture with 1 : 4-dibenzoylthiosemicarbazide prepared as described by Fehrenbach and Stolle (*J. pr. Chem.*, 1929, **122**, 289) (Found : C, 60·7; H, 4·4; N, 14·1. Calc. for $C_{15}H_{13}O_2N_3S$: C, 60·3; H, 4·3; N, 14·1%).

The following compounds were prepared in very good yield by method (*c*) from the corresponding thiosemicarbazides. 1-p-*Chlorobenzoylthiosemicarbazide* (II; R = *p*-ClC_6H_4) crystallised in colourless glistening needles, m. p. 218—220°, from aqueous alcohol (Found : C, 42·0; H, 3·2; S, 13·9. $C_8H_8ON_3ClS$ requires C, 41·8; H, 3·5; S, 13·9%); a residue insoluble in aqueous alcohol, crystallised from 2-ethoxyethanol, gave colourless leaflets of 1 : 2-di-*p*-chlorobenzoylhydrazine, m. p. 292° not depressed by admixture with a specimen prepared as described by Stolle (*Ber.*, 1912, **45**, 280) (Found : Cl, 22·5. Calc. for $C_{14}H_{10}O_2N_2Cl_2$: Cl, 22·9%). 1-p-*Methoxybenzoylthiosemicarbazide* (II; R = *p*-MeO·C_6H_4) crystallised in small regular prisms or needles, m. p. 236° (decomp.), from 2-ethoxyethanol (Found : C, 48·0; H, 4·7; N, 18·4. $C_9H_{11}O_2N_3S$ requires C, 48·0; H, 4·9; N, 18·7%). 1-p-*Nitrobenzoylthiosemicarbazide* (II; R = *p*-NO_2·C_6H_4) crystallised in colourless needles, m. p. 219° (decomp.), from *n*-propyl alcohol (Found : C, 40·0; H, 3·3; S, 13·3. $C_8H_8O_3N_4S$ requires C, 40·0; H, 3·3; S, 13·4%); on concentration of the mother-liquors from the initial crystallisation, a solid separated which on crystallisation from 2-ethoxyethanol gave yellow leaflets of 1 : 2-di-*p*-nitrobenzoylhydrazine, m. p. 289° not depressed by this compound as prepared by the method of Curtius and Trachmann (*J. pr. Chem.*, 1895, **51**, 178) (Found : C, 51·2; H, 3·0; N, 17·0. Calc. for $C_{14}H_{10}O_6N_4$: C, 50·9; H, 3·0; N, 17·0%). 1-Benzoyl-4-phenylthiosemicarbazide crystallised in fine colourless needles, m. p. 166°, from alcohol, identical with a specimen prepared as described by Marckwald and Bott (*loc. cit.*) (Found : C, 61·8; H, 5·0. Calc. for $C_{14}H_{13}ON_3S$: C, 62·0; H, 4·8%). 1-p-*Methoxybenzoyl-4-phenylthiosemicarbazide* crystallised from alcohol in colourless hair-like needles, m. p. 184°, from alcohol (Found : C, 60·1; H, 4·9. $C_{15}H_{15}O_2N_3S$ requires C, 59·8; H, 5·0%). 1-Benzoyl-4-methylthiosemicarbazide crystallised in colourless silky needles, m. p. 195°, from alcohol, identical with a specimen prepared as described by Young and Oates (*loc. cit.*) (Found : C, 51·3; H, 5·0. Calc. for $C_9H_{11}ON_3S$: C, 51·7; H, 5·3%). 1-*Benzoyl*-4-iso-*propylthiosemicarbazide* crystallised in colourless needles, m. p. 175°, from alcohol (Found : C, 55·5; H, 6·4; S, 13·5. $C_{11}H_{15}ON_3S$ requires C, 55·7; H, 6·3; S, 13·5%). 1-p-*Methoxybenzoyl-4-methylthiosemicarbazide* crystallised in colourless needles, m. p. 210°, from 2-ethoxyethanol (Found : C, 50·6; H, 5·3. $C_{10}H_{13}O_2N_3S$ requires C, 50·3; H, 5·4%). 1-*Benzoyl*-2 : 4-*dimethylthiosemicarbazide* crystallised in colourless needles, m. p. 193° (decomp.), from aqueous alcohol (Found : C, 53·8; H, 5·6; S, 14·3. $C_{10}H_{13}ON_3S$ requires C, 53·8; H, 5·8; S, 14·4%). 1-p-*Methoxybenzoyl*-2 : 4-*dimethylthiosemicarbazide* crystallised in felted colourless needles, m. p. 192° (decomp.), from alcohol (Found : C, 52·2; H, 6·1; S, 12·9. $C_{11}H_{15}O_2N_3S$ requires C, 52·2; H, 5·9; S, 12·7%). 1-*Benzoyl*-4 : 4-*dimethylthiosemicarbazide* crystallised in colourless needles, m. p. 170°, from alcohol (Found : C, 54·0; H, 5·9; S, 14·3. $C_{10}H_{13}ON_3S$ requires C, 53·8; H, 5·8; S, 14·4%). 1-p-*Methoxybenzoyl*-4 : 4-*dimethylthiosemicarbazide* crystallised in colourless needles, m. p. 167°, from alcohol (Found : C, 52·2; H, 6·0; S, 12·8. $C_{11}H_{15}O_2N_3S$ requires C, 52·2; H, 5·9; S, 12·7%).

2-*Amino-5-phenyl*-1 : 3 : 4-*thiadiazole* (I; R = Ph).—1-Benzoylthiosemicarbazide (2·0 g.) was added to syrupy phosphoric acid (10 c.c.) stirred in an oil-bath at 120° during 10 minutes, stirring was continued 30 minutes, and the acid solution cooled and diluted with ice and water to 100 c.c. (there was no insoluble material, indicating complete absence of the triazole-thiol). The precipitate formed by adding excess

of ammonia solution was crystallised from aqueous alcohol, giving colourless square plates (1·0 g.), m. p. 224°, identical with 2-amino-5-phenyl-1 : 3 : 4-thiadiazole prepared by oxidation of benzaldehyde thiosemicarbazone (Young and Eyre, *loc. cit.*) (Found : C, 53·9; H, 4·1. Calc. for $C_8H_7N_3S$: C, 54·1; H, 4·0%). An exactly similar result was obtained by using sulphuric acid (20·0 c.c.) and water (2·0 c.c.) in place of the phosphoric acid. This compound (0·9 g.) in boiling acetic acid (15·0 c.c.) was treated with " perhydrol " (5·0 c.c.), and boiling continued for 20 minutes. The precipitate formed on diluting the product with water and making it alkaline, was collected and crystallised from aqueous alcohol, giving unchanged thiadiazole (0·5 g.), m. p. 224° (Found : S, 18·1. Calc. for $C_8H_7N_3S$: S, 18·1%). The compound (1·8 g.) was also boiled in alcohol (25 c.c.) with Raney nickel catalyst (5·0 g.) for 6 hours and recovered unchanged (1·1 g.), m. p. 224° (Found : S, 18·6%).

2-*Amino*-5-p-*methoxyphenyl*-1 : 3 : 4-*thiadiazole* (I; R = *p*-MeO·C_6H_4).—(*a*) 1-*p*-Methoxybenzoylthiosemicarbazide (2·3 g.) was treated with phosphoric acid as described above. After dilution of the reaction liquid with water, the solid was collected and washed. This material was free from sulphur and crystallised from water in colourless needles (0·3 g.), m. p. 181° not depressed by admixture with *p*-methoxybenzoic acid. The acid filtrate was basified with ammonia, and the precipitate collected and crystallised from alcohol, giving colourless prisms of the *thiadiazole* (0·6 g.), m. p. 190° (Found : C, 52·4; H, 4·2. $C_9H_9ON_3S$ requires C, 52·2; H, 4·4%). (*b*) The same compound was obtained by oxidation of *p*-methoxybenzaldehyde thiosemicarbazone as described by Young and Eyre for the benzaldehyde compound; m. p. 190° (Found : C, 52·3; H, 4·4%).

2-*Amino*-5-p-*nitrophenyl*-1 : 3 : 4-*thiadiazole* (I; R = *p*-NO_2·C_6H_4).—This *compound* formed golden yellow prisms, m. p. 254°, from 2-ethoxyethanol (using either phosphoric or sulphuric acid) (Found : C, 43·1; H, 2·8. $C_8H_6O_2N_4S$ requires C, 43·1; H, 2·7%). The acid solution after dilution was neutralised with potassium hydrogen carbonate, as the product is unstable in the presence of strong alkali.

The following compounds were obtained, usually by the action of phosphoric acid on the corresponding benzoylthiosemicarbazides. 2-Methylamino-5-phenyl-1 : 3 : 4-thiadiazole crystallised in large colourless prisms, m. p. 183°, from alcohol (using either phosphoric or sulphuric acid) (Found : C, 56·4; H, 4·7. Calc. for $C_9H_9N_3S$: C, 56·5; H, 4·7%). Young and Eyre (*loc. cit.*) obtained this compound by oxidation of the corresponding thiosemicarbazone and give m. p. 183°. 2-*Methylamino*-5-p-*methoxyphenyl*-1 : 3 : 4-*thiadiazole* crystallised in colourless needles, m. p. 150°, from alcohol (*p*-methoxybenzoic acid also isolated) (Found : C, 54·3; H, 4·9. $C_{10}H_{11}ON_3S$ requires C, 54·3; H, 5·0%). 2-*Methylimino*-5-*phenyl*-3-*methyl*-2 : 3-*dihydro*-1 : 3 : 4-*thiadiazole* (VI; R = Ph, R′ = Me) was obtained as a colourless oil, b. p. 120—122°/1·0 mm., $n_D^{25°}$ 1·6340 (Found : C, 58·2; H, 5·7; S, 15·4. $C_{10}H_{11}N_3S$ requires C, 58·5; H, 5·4; S, 15·6%); the *picrate* crystallised from alcohol–2-ethoxyethanol in greenish-yellow hexagonal plates, m. p. 208° (Found : C, 44·0; H, 3·4; S, 7·7. $C_{10}H_{11}N_3S,C_6H_3O_7N_3$ requires C, 44·2; H, 3·2; S, 7·4%). 2-*Methylimino*-5-p-*methoxyphenyl*-3-*methyl*-2 : 3-*dihydro*-1 : 3 : 4-*thiadiazole* (VI; R = *p*-MeO·C_6H_4, R′ = Me) crystallised in colourless leaflets, m. p. 112°, from alcohol (Found : C, 56·0; H, 5·7. $C_{11}H_{13}ON_3S$ requires C, 56·2; H, 5·5%). 2-*Dimethylamino*-5-*phenyl*-1 : 3 : 4-*thiadiazole* crystallised in large colourless needles, m. p. 98°, from light petroleum (b. p. 60—80°) with a little benzene (Found : C, 58·5; H, 5·2; S, 15·2. $C_{10}H_{11}N_3S$ requires C, 58·5; H, 5·4; S, 15·6%).

2-*Dimethylamino*-5-p-*methoxyphenyl*-1 : 3 : 4-*thiadiazole*.—(*a*) This *compound*, obtained as above, crystallised in large pointed colourless needles, from alcohol, m. p. 124° (Found : C, 56·1; H, 5·4; N, 17·5. $C_{11}H_{13}ON_3S$ requires C, 56·2; H, 5·5; N, 17·9%).

(*b*) 4 : 4-Dimethylthiosemicarbazide (Jensen, *J. pr. Chem.*, 1941, **159**, 189) (11·9 g.) and *p*-methoxybenzaldehyde (13·6 g.) were heated gently in alcohol (50 c.c.) for 18 hours. The solid which separated was crystallised from alcohol, giving yellow leaflets of the *thiosemicarbazone* (8·6 g.), m. p. 130° (Found : C, 53·3; H, 6·4. $C_{11}H_{15}ON_3S$ requires C, 55·7; H, 6·3%). This compound was oxidised as described by Young and Eyre (*loc. cit.*), giving the same thiadiazole as in (*a*), m. p. 124° (Found : C, 55·9; H, 5·2%).

2-*Benzamido*-5-*phenyl*-1 : 3 : 4-*thiadiazole*.—1 : 4-Dibenzoylthiosemicarbazide (3·0 g.) and syrupy phosphoric acid (10 c.c.) gave this compound, which crystallised from 2-ethoxyethanol in silky needles (2·4 g.) m. p. 235° (Found : S, 11·3. Calc. for $C_{15}H_{11}ON_3S$: S, 11·4%). The compound was boiled with concentrated hydrochloric acid and 2-ethoxyethanol for 12 hours, giving 2-amino-5-phenyl-1 : 3 : 4-thiadiazole, which crystallised from aqueous alcohol in small rectangular plates, m. p. 224° not depressed by this compound as prepared above (Found : C, 54·1; H, 3·7%).

Dehydration of 1-*Benzoyl*-4-*phenylthiosemicarbazide*.—(*a*) The benzoyl compound (2·7 g.) was dehydrated in the usual way with phosphoric acid (10 c.c.), and after dilution with ice and water (250 c.c.) the mixture was made alkaline with concentrated sodium hydroxide solution. The solid was collected and crystallised from alcohol, giving long colourless needles (1·0 g.), m. p. 198°, of 2-phenylamino-5-phenyl-1 : 3 : 4-thiadiazole (Young and Eyre obtained this compound by oxidation of the corresponding thiosemicarbazone and gave m. p. 199°) (Found : C, 66·3; H, 4·4. Calc. for $C_{14}H_{11}N_3S$: C, 66·4; H, 4·3%). The original alkaline filtrate was acidified, and the precipitate crystallised from alcohol, giving long colourless needles of 3 : 4-diphenyl-4 : 1 : 2-triazole-5-thiol (0·5 g.), m. p. 282° (Marckwald and Bott give m. p. 187°; a misprint for 287°?) (Found : C, 66·4; H, 4·2; S, 13·1. Calc. for $C_{14}H_{11}N_3S$: C, 66·4; H, 4·3; S, 12·7%). When the above triazole (1·2 g.) was oxidised with " perhydrol " (5·0 c.c.) in boiling acetic acid (15 c.c.), 3 : 4-diphenyl-4 : 1 : 2-triazole was formed, which crystallised from light petroleum (b. p. 60—80°) in colourless needles (0·5 g.), m. p. 136° (Marckwald and Bott give m. p. 142°) (Found : C, 76·2; H, 5·0. Calc. for $C_{14}H_{11}N_3$: C, 76·0; H, 5·0%). When the thiadiazole (1·2 g.) was treated with " perhydrol " in the same way, unchanged starting material was recovered (0·75 g.), m. p. 198° (Found : S, 12·9%).

(*b*) The benzoyl compound (5·4 g.) and acetyl chloride (3·1 g.) were mixed ice-cold. A vigorous reaction took place, and after 5 minutes' warming on the water-bath, water (250 c.c.) was added. Concentrated sodium hydroxide solution was added to alkalinity, and the solid collected and crystallised from alcohol, giving the thiadiazole (2·2 g.), m. p. 200° (Found : S, 12·8. Calc. for $C_{14}H_{11}N_3S$: S, 12·7%). The alkaline filtrate was made acid with concentrated hydrochloric acid, and the triazole collected and crystallised from alcohol (0·25 g., m. p. 282°) (Found : S, 12·4%).

(*c*) When benzoyl chloride (5·6 g.) was used in place of acetyl chloride in (*b*) above, the thiadiazole

was isolated as previously (1·0 g.), m. p. 198° (Found : S, 13·1%). The precipitate obtained by acidifying the alkaline solution was stirred for 1 hour with 10% potassium hydrogen carbonate solution (to remove benzoic acid), and the insoluble triazole collected and crystallised from alcohol (1·6 g.), m. p. 284° (Found : S, 13·0%).

Dehydration of 1-*Benzoylthiosemicarbazide.*—(*a*) 1-Benzoylthiosemicarbazide (10·0 g.) and acetyl chloride (8·0 g.) were mixed ice-cold and cautiously heated under reflux. When the vigorous reaction subsided, heating was continued for 15 minutes, and water (200 c.c.) added, followed by 5N-sodium hydroxide solution until the mixture was strongly alkaline. The insoluble material was collected and crystallised from aqueous alcohol, giving colourless plates (1·8 g.), m. p. 224°, of 2-amino-5-phenyl-1 : 3 : 4-thiadiazole. The alkaline solution was precipitated with acid, and the 2-acetamido-5-phenyl-1 : 3 : 4-thiadiazole (7·5 g.), m. p. 278°, collected and boiled with water to extract any 3-phenyl-1 : 2 : 4-triazole-5-thiol. None of the latter compound was found, and the residue was crystallised from 2-ethoxyethanol, giving colourless needles (4·6 g.), m. p. 281—282° (Found : S, 14·6. Calc. for $C_{10}H_9ON_3S$: S, 14·6%). The constitution of this compound was established by hydrolysis. The acetamido-compound (1·0 g.), 2-ethoxyethanol (20 c.c.), and concentrated hydrochloric acid (5 c.c.), refluxed together for 18 hours, gave 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (0·5 g.), m. p. 225° (Found : S, 18·3%).

(*b*) With benzoyl chloride (14·0 g.) in place of acetyl chloride in the above experiment, 2-benzamido-5-phenyl-1 : 3 : 4-thiadiazole (3·9 g.), m. p. 235° (Found : S, 11·3%), and 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (3·2 g.), m. p. 225° (Found : S, 17·9%), were obtained. Benzoic acid (6·5 g.) was separated from the benzamido-compound with potassium hydrogen carbonate solution, but no 3-phenyl-1 : 2 : 4-triazole-5-thiol was found.

Dehydration of 1-*Benzoyl-4-methylthiosemicarbazide.*—(*a*) This compound (2·1 g.) and acetyl chloride (1·6 g.), on reaction together as in (*a*) above, gave 2-methylaminophenyl-1 : 3 : 4-thiadiazole (1·1 g.), m. p. 183° (Found : S, 16·8%). (*b*) The benzoyl compound (10·5 g.) and benzoyl chloride (14·0 g.) on reaction as in (*b*) above gave a mixture ; the portion soluble in N-sodium hydroxide gave 3-phenyl-4-methyl-4 : 1 : 2-triazole-5-thiol (0·55 g.), m. p. 166° not depressed by a specimen prepared as described by Young and Eyre (see below) (Found : S, 16·6. Calc. for $C_9H_9N_3S$: S, 16·8%), and benzoic acid (6·4 g.) separated by potassium hydrogen carbonate ; the residue insoluble in alkali was extracted with N-hydrochloric acid, leaving 2-*benzomethylamido-5-phenyl*-1 : 3 : 4-*thiadiazole*, which crystallised from alcohol in large colourless prisms (5·5 g.), m. p. 135° (Found : C, 65·1 ; H, 4·6 ; S, 11·0. $C_{16}H_{13}ON_3S$ requires C, 65·1 ; H, 4·4 ; S, 10·7%). (The constitution of this compound was confirmed by hydrolysis with acid to 2-methylamino-5-phenyl-1 : 3 : 4-thiadiazole, m. p. 182°, as described above for 2-acetamido-5-phenyl-1 : 3 : 4-thiadiazole.) The acid extract was made alkaline and gave 2-methylamino-5-phenyl-1 : 3 : 4-thiadiazole (1·4 g.), m. p. 182°. When the triazole (0·5 g.) was oxidised with " perhydrol " (2·5 c.c.) in acetic acid (5 c.c.), 3-phenyl-4-methyl-4 : 1 : 2-triazole was obtained, and crystallised from benzene in colourless needles (0·25 g.), m. p. 116° (Found : C, 68·2 ; H, 6·3. Calc. for $C_9H_9N_3$: C, 67·9 ; H, 5·7%). Under the same conditions the thiadiazole was recovered unchanged (0·4 g.), m. p. 183°.

3-*Phenyl*-1 : 2 : 4-*triazole-5-thiol* (III ; R = Ph).—1-Benzoylthiosemicarbazide (3·9 g.) was added to a solution of sodium (1·5 g.) in alcohol (50 c.c.) and the whole gently heated under reflux for 12 hours. After evaporation to dryness under reduced pressure, the residue was dissolved in water (100 c.c.), filtered (charcoal), and acidified with 10% acetic acid. The precipitate was collected, washed, and dried (3·4 g. ; m. p. 240—245°), and crystallised from water in colourless leaflets (2·8 g.), m. p. 256° not depressed by 3-phenyl-1 : 2 : 4-triazole-5-thiol prepared as described in Part I (Found : C, 54·4 ; H, 3·8 ; S, 18·2. Calc. for $C_8H_7N_3S$: C, 54·2 ; H, 4·0 ; S, 18·1%). The same result was obtained by using piperidine (2·5 c.c.) in place of sodium ethoxide, but longer reaction time was necessary with pyridine.

The following were prepared in analogous experiments : all had m. p.s not depressed by the compounds prepared as previously. 3-*p*-Methoxyphenyl-1 : 2 : 4-triazole-5-thiol (III ; R = *p*-MeO·C_6H_4) crystallised in stout needles from aqueous alcohol, m. p. 257° (Found : C, 52·1 ; H, 4·2 ; S, 15·4. Calc. for $C_9H_9ON_3S$: C, 52·2 ; H, 4·35 ; S, 15·5%). 3-*p*-Chlorophenyl-1 : 2 : 4-triazole-5-thiol (III ; R = *p*-C_6H_4Cl) crystallised as a microcrystalline powder from aqueous alcohol, m. p. 296—298° (Found : C, 45·6 ; H, 3·0 ; S, 14·9. Calc. for $C_8H_6N_3ClS$: C, 45·4 ; H, 2·8 ; S, 15·1%). 3-Phenyl-4-methyl-4 : 1 : 2-triazole-5-thiol (V ; R = Ph, R′ = Me) crystallised in flattened needles from alcohol, m. p. 166° (Found : C, 56·3 ; H, 4·6%). 3-*p*-Methoxyphenyl-4-methyl-4 : 1 : 2-triazole-5-thiol (V ; R = *p*-MeO·C_6H_4, R′ = Me) crystallised in long needles from aqueous alcohol, m. p. 176—178° (Found : C, 54·7 ; H, 4·9. $C_{10}H_{11}ON_3S$ requires C, 54·3 ; H, 5·0%). This compound was also obtained, m. p. 176°, by the method of Young and Eyre (*loc. cit.*) by heating 1-*p*-methoxybenzoyl-4-methylthiosemicarbazide at 200° (Found : C, 54·1 ; H, 4·7%). 3 : 4-Diphenyl-4 : 1 : 2-triazole-5-thiol (V ; R = R′ = Ph) crystallised in silky needles from alcohol, m. p. 282° (Found : S, 12·7%).

1 : 4-*Dibenzoylthiosemicarbazide.*—1-Benzoylthiosemicarbazide (3·9 g.) was stirred in pyridine (20 c.c.) and treated with benzoyl chloride (3·8 g.) below 0°. After 12 hours' standing, water (100 c.c.) was added, and the pyridine removed under reduced pressure. The precipitate was collected and ground with N-sodium hydroxide solution (50 c.c.), and the yellow sodium salt was collected, washed with a little water, and ground with N-hydrochloric acid until decolorised. The solid was collected, washed, and crystallised from alcohol, giving 1 : 4-dibenzoylthiosemicarbazide as colourless plates (0·65 g.) ; m. p. 176° (Found : S, 10·6. Calc. for $C_{15}H_{13}O_2N_3S$: S, 10·7%). The original alkaline solution was precipitated with acid, and the flocculent precipitate collected (free from sulphur) and crystallised from water containing a little alcohol, giving long felted needles (1·1 g.), m. p. 236° not depressed by 1 : 2-dibenzoylhydrazine as prepared by the method of Autenrieth and Spiess (*Ber.*, 1901, **34**, 187) (Found : C, 69·8 ; H, 4·6 ; N, 12·0. Calc. for $C_{14}H_{12}O_2N_2$: C, 70·0 ; H, 5·0 ; N, 11·7%).

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252. *Covalency, Co-ordination, and Chelation. Part II. Complex-formation by the Trimethylplatinic Group.*

By W. J. Lile and R. C. Menzies.

New compounds are described indicating that in its trimethyl compounds a co-ordination number of 6 is as characteristic a property of quadrivalent platinum as is a co-ordination number of 4 characteristic of tervalent gold (see Burawoy, Gibson, and Holt, *J.*, 1935, 1024).

In Part I (*J.*, 1933, 1290) it was pointed out that the alkylated derivatives of the elements 78 to 82—platinum to lead—only formed chelated compounds in those cases where the effective co-ordination number exceeded the normal valency. The dialkyls and alkyl halides of mercury, where the valency and co-ordination numbers are both two, and the tetra-alkyls and trialkyl halides of lead (both four) are unimolecular, and attempts to make their chelate derivatives failed. The halides of trimethylplatinum, dialkylgold, and dialkylthallium, on the other hand, are all associated in benzene solution, indicating that the effective co-ordination number is greater in each case than the normal valency functioning, and preparation of their chelate derivatives is easy (*J.*, 1928, 565, 1288; Gibson and Simonsen, *J.*, 1930, 2532; Brain and Gibson, *J.*, 1939, 766). The trimethylplatinum and dialkylgold halides are, however, difficult to make.

To such alkylated groups the name pseudo-atoms is often given and many of them resemble the atoms and, when charged, the ions of inorganic chemistry in their behaviour and compounds. According to Grimm (Geiger and Scheel's "Handbuch der Physik", Band XXIV, p. 519), similar atoms and pseudo-atoms are of such a nature that other atoms or groups brought into their neighbourhood are subjected to similar fields. The more obvious and earliest observed indications of such fields are acid or alkaline reaction, colour, melting point, solubility, and the formation or non-formation of ions. The atoms and ions of the alkali metals and of the alkaline-earth metals were thus soon recognised as two groups of similar atoms and two groups of similar derived ions. As regards organic and organometallic pseudo-atoms, Grimm's definition is a restatement of Berzelius's theory of compound radicals, of which a striking example was Bunsen's work on cacodyl (*Annalen*, 1841, **37**, 1). The ammonium and substituted-ammonium ions and the similar phosphonium and arsonium ions are examples of ions resembling those formed from the elements of Group I.

Less familiar is ethylboric acid (Khotinski and Melamid, *Ber.*, 1909, **42**, 3095), which resembles the compounds of the preceding element beryllium in having a sweet taste (Vauquelin, *Ann. Chim.*, 1798, **26**, 169, 173; Höber and Kiesow, *Z. Phys. Chem.*, 1898, **27**, 609). Ethylstannonic acid (Druce, *J.*, 1921, **119**, 758) is amphoteric and bears a strong resemblance to the hydroxides of aluminium, gallium, and indium. Diethylgold bromide (Pope and Gibson, *J.*, 1907, **91**, 2064) resembles the halides of univalent copper and silver in being colourless and insoluble in water, while monoethylgold dibromide resembles the salts of bivalent copper in being coloured and soluble in water and of bivalent silver in being coloured. The methyl-gold compounds as far as described are similar (Brain and Gibson, *J.*, 1939, 762). Penta-, tetra-, and tri-phenylchromium hydroxides are strong monoacid bases (Hein, *Ber.*, 1921, **54**, 1923; 1924, **57**, 8; Hein and Markert, *Ber.*, 1928, **61**, 2255), as is diphenyliodonium hydroxide.

Quite as striking as the above is the resemblance between some trimethylplatinic derivatives and those of silver. Trimethylplatinic nitrate (Pope and Peachey, *J.*, 1909, **95**, 571) is soluble in water, markedly deliquescent, and colourless. The chloride, also colourless, is insoluble in water. The iodide, obtained by Pope and Peachey as an orange sandy powder, was later obtained by Wiltshire (*J.*, 1933, 1294) as a white precipitate on adding potassium iodide to a solution in aqueous acetic acid of trimethylplatinic acetylacetone. Apart from the colour, both forms are similar under the microscope and are insoluble in water. Here again the derived pseudo-atom appears to belong to a lower group of the Periodic System than does the parent central atom. Trimethylplatinic iodide also resembles silver iodide in forming an addition compound with ammonia (Pope and Peachey, *loc. cit.*, p. 573), *viz.*, diamminotrimethylplatinic iodide, sparingly soluble in water, in which, as indicated by these authors, the metal is 6-covalent. This was again evident from the stable association of trimethylplatinic acetylacetone into double molecules in benzene (*J.*, 1933, 21) and is now further confirmed by the preparation of *dipyridinotrimethylplatinic iodide*, *2 : 2′-dipyridyltrimethylplatinic iodide*, *monoethylenediaminotrimethylplatinic iodide*, and *sesquiethylenediaminotrimethylplatinic iodide*, ethylenediamine being the only base from which two compounds were obtained. All four compounds are colourless except that the second, made from orange trimethylplatinic iodide, is pale yellow. The first

two are insoluble, and the last two soluble in water, the mono-compound more readily. A possible structure for the last is shown in the inset: it is reminiscent of that of iron enneacarbonyl (Powell and Ewens, *J.*, 1939, 289). Both trimethylplatinic acetylacetone and the above dipyridyl compound are insoluble in water, but 2 : 2′-*dipyridyltrimethylplatinic acetylacetone* dissolves. In this compound there are seven potential co-ordinating addenda competing for six places, one nitrogen of the dipyridyl, or one oxygen of the acetylacetone gets left out, and, hanging loose, attaches itself to the solvent, conferring solubility on the whole molecule, as does a carbohydrate residue on a condensed system of aromatic rings.

Detailed consideration of the structural formulæ of the compounds now described, as also of the trimethylplatinic derivatives of the halogens and β-diketones, is deferred until their molecular weights in solution have been determined. A quantitative examination by *X*-ray analysis of any found to give suitable crystals would also be welcome.

Trimethylplatinic chloride is the only compound for which both determinations have been attempted, it having been shown in Part I (*loc. cit.*, p. 1293) that its degree of association in benzene solution lies between 1·71 and 1·95, while Pauling (" Nature of the Chemical Bond," 1940, p. 102) points out that an incomplete structure of trimethylplatinic chloride indicates that tetramers $Pt_4(CH_3)_{12}Cl_4$ exist in the crystals, with each platinum atom forming six octahedral bonds.

Summarising, it may be said that in the case of platinum also combination with methyl groups alters the more obvious properties, on the basis of which classification of the elementary atoms and ions into groups was originally based, to those characteristic of a lower group, but that the less obvious but fundamental co-ordination number remains unchanged.

Experimental.

(Analyses marked with an asterisk are by Dr. Schoeller of Berlin.)

A theoretical yield (1·65 g.) of the white trimethylplatinic iodide used in some of the preparations described below was obtained by adding 5 g. of potassium iodide in 30 c.c. of water to a solution in hot dilute acetic acid of 1·65 g. of trimethylplatinic dipropionylmethane (*J.*, 1933, 22).

Dipyridinotrimethylplatinic iodide was obtained by heating 0·13 c.c. (excess) of pyridine with 0·1 g. of orange trimethylplatinic iodide in 10 c.c. of benzene. The almost colourless solution, after evaporation to about 2 c.c., was nucleated from long colourless prisms left on evaporating a drop on a slide and readily crystallised; m. p. 168° (without decomp.) (Found: N, 5·35. $C_3H_9PtI,2C_5H_5N$ requires N, 5·33%). No data were obtained for platinum, the compound decomposing explosively on heating.

2 : 2′-*Dipyridyltrimethylplatinic iodide* separated as colourless crystals (0·68 g., 95%) when the golden-yellow solution obtained from 0·212 g. (1 equiv.) of dipyridyl and 0·5 g. (1 equiv.) of colourless trimethylplatinic iodide in hot benzene was boiled for 1 min.; m. p. 273° (decomp.; darkening slowly above 225°) (Found: C, 30·0*; H, 3·30*; N, 5·40*; I, 24·8, 24·2; Pt, 37·2*. $C_3H_9IPt,C_{10}H_8N_2$ requires C, 29·8; H, 3·27; N, 5·35; I, 24·25; Pt, 37·3%). The iodine was determined by titrating an acetone solution with 0·1N-aqueous silver nitrate, potassium dichromate, which produces no precipitate with the dipyridyl compound, being used as internal indicator. From the acetone–water solution was obtained a bright yellow solid soluble in alcohol, acetone, and water; it crystallised from boiling alcohol in long, almost colourless needles, darkening above 220°, and fusing, with decomposition at 246°. This is believed to be dipyridyltrimethylplatinic nitrate, but analyses were not good.

The dipyridyl iodide after recrystallisation from acetone gave analytical figures high for C and H and low for N, indicating combination with the solvent, and its molecular weights in boiling chloroform decrease with increasing concentration, similarly indicating reaction with the solvent (cf. Biltz, *Annalen*, 1904, **331**, 334).

The precipitation of silver iodide from acetone solutions of this iodide further suggests the existence of some compound such as $[PtMe_3,dipy,COMe_2]I$.

On refluxing 0·2 g. of orange trimethylplatinic iodide with 0·17 g. (2 equivs.) of dipyridyl in an attempt to prepare a sesquidipyridyl compound similar to the ethylenediamine compound, the above iodide, m. p. 272° (Found: N, 5·1; Pt, 38·1%), was again obtained. This iodide is apparently unchanged on boiling with dilute acetic acid, hydrochloric acid, 2N-ammonia, or sodium hydroxide. It is, however, attacked by ethylenediamine (see p. 1170), and decomposed by boiling alcoholic potash.

Monoethylenediaminotrimethylplatinic iodide was obtained by refluxing 1 g. of orange trimethylplatinic iodide with 0·08 c.c. (0·5 equiv.) of anhydrous ethylenediamine in 25 c.c. of benzene for 2 hours. The white solid (m. p. 204°) was separated from the pale yellow solution, and concentration of the filtrate to about one-third gave dull orange crystals, m. p. 206°. Recrystallised from water, in which it is more soluble than the sesqui-compound described below, the normal iodide was obtained as square plates and prisms; m. p. 204 (decomp.) (Found: Pt, 45·2; N, 6·9. $C_3H_9PtI,C_2H_8N_2$ requires Pt, 45·7; N, 6·7%). From the benzene mother-liquors more of this compound was recovered mixed with unchanged trimethylplatinic iodide. It is unchanged (m. p. and mixed m. p.) on boiling with dipyridyl in benzene.

Sesquiethylenediaminotrimethylplatinic iodide (0·63 g., white needles, darkening above 230° and melting at 273° with formation of a platinum mirror) was obtained from 0·73 g. of orange trimethylplatinic iodide and excess of ethylenediamine dissolved in benzene. Water was added and after

evaporation of the benzene the product was recrystallised from water (Found: C, 16·05*; H, 4·58*; N, 8·5*; Pt, 42·5*. $2C_5H_5PtI,3C_5H_5N_5$ requires C, 15·76; H, 4·63; N, 9·2; Pt, 42·7%).

Action of ethylenediamine on dipyridyltrimethylplatinic iodide. 0·5 G. of the dipyridyl compound, from orange trimethylplatinic iodide, was dissolved in chloroform, 0·08 c.c. of ethylenediamine (1 equiv.) added to the hot solution, and the mixture heated under reflux. On standing, colourless crystals were produced. A drop of the clear solution, shaken with water and an aqueous solution of potassium mercuri-iodide, gave a white flocculent precipitate, indicating the presence of free dipyridyl. No such precipitate is produced by a solution of the dipyridyl compound. Rosettes and twinned needles of the sesqui-compound were obtained on recrystallisation from water; m. p. 266° (darkening above 240°) (Found: Pt, 41·9; N, 8·94%).

0·5 G. of the dipyridyl compound were then treated in cold chloroform with 0·06 c.c. of ethylenediamine, and the solution allowed to evaporate at room temperature. Pale yellow rhombic plates and a dark orange substance were deposited. These were separated into an acetone-soluble portion, yellow needles [m. p. 274° (decomp.) and mixed m. p. with the dipyridyl iodide 273°], and an acetone-insoluble portion. The latter after recrystallisation from water melted at 270° without decomposition. Mixed with the dipyridyl compound it melted at 246°, and mixed with the sesqui-compound at 271°. The presence of the monoethylenediamino-iodide was not observed.

Dipyridyltrimethylplatinic acetylacetone was obtained as pale yellow hexagonal plates and prisms on allowing to evaporate at room temperature the golden-yellow solution obtained by dissolving 0·17 g. of trimethylplatinic acetylacetone and 0·039 g. (0·5 equiv.) of dipyridyl in 10 c.c. of benzene. Crystallised from hexane–benzene, this gave dull orange needles, m. p. 143° (decomp.; darkening above 120°, with signs of softening) (Found: N, 5·5. $C_5H_{16}O_2Pt,C_{10}H_8N_2$ requires N, 5·6%). The same compound was also formed by heating the dipyridyl iodide (0·32 g.) and thallous acetylacetone (0·185 g.) under reflux in benzene, filtering and evaporating the solvent; crystals and a brown sticky mass were obtained, which was stirred with benzene and alcohol, and filtered from insoluble material. On evaporation, dull orange needles were obtained; m. p. 142° (decomp.; darkening above 115° with slight softening); mixed m. p. with the above acetylacetone compound 142—143° (decomp.). This compound is fairly soluble in water.

When the acetylacetone compound was dissolved in water, and a little acetic acid and excess of potassium iodide added, a white curdy precipitate was produced; after being washed and dried, this darkened slightly above 230° and had m. p. 268° (decomp.) and mixed m. p. with the dipyridyl iodide 270°. We thus have the following parallel pairs of reactions, all of which have been carried out:

$$\begin{array}{ccc} (CH_3)_3PtI & \xrightarrow{\text{dipy}} & (CH_3)_3PtI,\text{dipy} \\ {\scriptstyle C_5H_7O_2Tl}\downarrow\uparrow{\scriptstyle KI} & & {\scriptstyle C_5H_7O_2Tl}\downarrow\uparrow{\scriptstyle KI} \\ (CH_3)_3Pt,C_5H_7O_2 & \xrightarrow{\text{dipy}} & (CH_3)_3Pt,\text{dipy},C_5H_7O_2 \end{array}$$

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253. *The Constitution of ψ-Santonin. Part VI. Experiments on ψ-Santonic Acid.*

By WESLEY COCKER and CYRIL LIPMAN.

Experiments performed on ψ-santonic acid are described and a tentative structure (I) is suggested for this compound.

WHEN ψ-santonin is treated with cold concentrated hydrochloric acid, a bright yellow solution is obtained from which an acid subsequently separates (Clemo and Cocker, *J.*, 1947, 533). This dextrorotatory acid, to which the name ψ-santonic acid (I) has been given (Cocker, Cross, and Lipman, this vol., p. 959), may also be obtained in greater yield when 20% hydrochloric acid is employed, although concentrations as low as 1% initiate the formation of the acid. Cold 50% sulphuric acid is also effective.

The acid rapidly turns yellow on exposure to air in a manner reminiscent of (−)-santonin.

Analyses give the formula, $C_{15}H_{22}O_5$, which suggests the simple hydrolysis of the lactone ring of ψ-santonin ($C_{15}H_{20}O_4$), but this is not the case. ψ-Santonic acid yields a *phenylhydrazone* and a 2 : 4-*dinitrophenylhydrazone* with difficulty, and, whilst it has not been made to yield a piperonylidene derivative, it yields a *derivative* with *o*-aminobenzaldehyde which is indicative of the presence of a keto-methylene group. We have been unable to obtain a semicarbazone or an oxime, either by the usual method or by the method of Haller and La Forge (*J. Org. Chem.*, 1936, **1**, 38; cf. Dutcher and Winterstein, *J. Amer. Chem. Soc.*, 1939, **61**, 1998, and others), and this is probably due to the presence of the polarisable C:C·C:O group.

ψ-Santonic acid possesses two ethylenic groups, since (*a*) two atoms of oxygen are absorbed when the acid is titrated with perbenzoic acid and a *diepoxide* (a lactone), $C_{15}H_{20}O_6$, is produced, and (*b*) it readily absorbs two molecules of hydrogen in presence of palladised charcoal and *tetrahydro-ψ-santonic acid* results. This tetrahydro-acid was obtained as a mono-hydrated form, $C_{15}H_{24}O_4,H_2O$, m. p. 191—192°, and as a non-hydrated form, m. p. 198°; both yielded the same non-hydrated *methyl tetrahydro-ψ-santonate*, but we have been unable to obtain an ester of ψ-santonic acid itself. Tetrahydro-ψ-santonic acid yields an unhydrated *oxime* readily, and a *derivative*, $C_{22}H_{27}O_3N$, with *o*-aminobenzaldehyde. Both of these compounds are acidic, and the latter is also basic. Reduction of ψ-santonic acid in presence of Adams platinic oxide catalyst yields the alcohol, *hexahydro-ψ-santonic acid*, $C_{15}H_{24}O_4$, with uptake of six atoms of hydrogen. Acetylation of this alcohol yields an *acetate*, $C_{17}H_{26}O_4$, which is also a lactone.

ψ-Santonic acid loses two molecules of water and undergoes lactonisation when heated above its melting point, yielding the dextrorotatory *anhydro-ψ-santonic acid*, $C_{15}H_{18}O_3$, which is unaffected by cold concentrated hydrochloric acid but is converted into (+)-β-desmotropo-ψ-santonin (Cocker, Cross, and Lipman, *loc. cit.*) on warming with 50% sulphuric acid. The lactone possesses two ethylenic bonds, since on hydrogenation in presence of palladised charcoal it yields *tetrahydroanhydro-ψ-santonic acid*, $C_{15}H_{22}O_3$, the analysis being confirmed by the absorption of four atoms of hydrogen per mol. of lactone during the reduction. This tetrahydro-compound yields a 2 : 4-*dinitrophenylhydrazone*. Reduction of anhydro-ψ-santonic acid in presence of Adams platinic oxide yields the alcohol, *hexahydroanhydro-ψ-santonic acid*, $C_{15}H_{24}O_3$, with uptake of six atoms of hydrogen and reduction of the carbonyl group.

When ψ-santonin is left in contact with concentrated hydrochloric acid for long periods it yields a *compound*, $C_{15}H_{23}O_5Cl$, which is probably a hydrochloride of ψ-santonic acid.

ψ-Santonin, $C_{15}H_{20}O_4$, possesses only one ethylenic bond (see earlier publications in this series) and this is confirmed by the production of a *monoepoxide* on treatment with perbenzoic acid, whereas ψ-santonic acid, $C_{15}H_{22}O_5$, obviously possesses two such linkages. It is probable, therefore, that ψ-santonin loses a molecule of water (presumably from the C_1–C_{10} linkage) on treatment with mineral acid. The bond so formed can undergo migration. At the same time the lactone ring is hydrolysed, thus absorbing a molecule of water. It is, therefore, concluded that the ψ-santonic acid described is a monohydrated compound, $C_{15}H_{20}O_4,H_2O$, and this is confirmed by the production of a hydrated and an anhydrous tetrahydro-compound, an anhydrous *oxime* of the tetrahydro-compound, and an anhydrous ester of the latter compound.

ψ-Santonic acid shows an ultra-violet light absorption maximum at 2345 A. (log ε 4·2) and an inflexion at 3200 A. (log ε 2·3), but tetrahydro-ψ-santonic acid and its anhydro-compound has only one maximum (at 2900 A., log ε 1·7), this probably being due to an isolated keto-group. It is clear, therefore, that ψ-santonic acid is an αβ-unsaturated ketone, and the work of Woodward (*J. Amer. Chem. Soc.*, 1941, **63**, 1123), Booker, Evans, and Gillam (*J.*, 1940, 1453), and others suggests that it is a disubstituted αβ-unsaturated ketone possessing the group R·CO·CR':CHR'' or R·CO·CH:CR'R''. This evidence conflicts with some of the chemical evidence already described. The fact that ψ-santonic acid forms a derivative with *o*-aminobenzaldehyde would seem to preclude the existence of an αβ-unsaturated keto-group, but, under the conditions of the reaction, migration of the double bond from the C_2–C_3 to the C_1–C_2 position is possible. From the ultra-violet light absorption, however, it appears that there is a substituent, presumably methyl, at either C_2 or C_3. A methyl group at C_3 is contraindicated by the formation of a derivative with *o*-aminobenzaldehyde, not only by ψ-santonic acid but also by its tetrahydro-derivative. A compound with a methyl group at C_2 would presumably give 3 : 4-dimethyl-1-naphthol by aromatisation and dehydrogenation unless migration of methyl were to take place during these processes, whereas 2 : 4-dimethyl-1-naphthol is obtained (cf. Clemo and Cocker, *loc. cit.* and Cocker, Cross, and Lipman, *loc. cit.*). The following evidence suggests that the methyl group is at the angular position, C_5, as in ψ-santonin. When tetrahydro-ψ-santonic acid is reduced under Clemmensen conditions, a gum is obtained which on dehydrogenation yields an oil, the picrate of which is identical with that of 1-methyl-7-ethyl-naphthalene (Harvey, Heilbron, and Wilkinson, *J.*, 1930, 423; Clemo and Haworth, *ibid.*, 2582). Thus a methyl group is lost in the dehydrogenation, a phenomenon characteristic of compounds possessing an angular methyl group, and a double bond at C_5–C_{10} is therefore impossible.

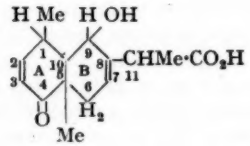
Infra-red light absorption measurements, kindly performed and interpreted by Imperial Chemical Industries, Ltd. (Billingham Division), show that ψ-santonic acid posesses absorption bands at 3500, 3430, and 3370 cm.$^{-1}$ indicating the presence of alcoholic ·OH group and/or

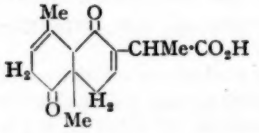
water of crystallisation in three different degrees of hydrogen bonding. A band at 3166 cm.$^{-1}$ indicates a carboxyl group involved in hydrogen bonding. A band at 1637 cm.$^{-1}$ indicates a double bond, probably conjugated with a carbonyl group, but not in a dienone system, a result in agreement with the ultra-violet light absorption data; and a band at 965 cm.$^{-1}$ probably indicates an isolated double bond. A strong band at 1696 cm.$^{-1}$ indicates the presence of a ketonic group or a carboxyl group or both.

Tetrahydro-ψ-santonic acid (hydrated) possesses infra-red absorption bands indicating the presence of carbonyl and hydroxy-groups, both involved in hydrogen bonding. It possesses a strong band at 1692 cm.$^{-1}$, probably corresponding to the carboxyl group. It also possesses a broad weak band from 1620 to 1660 cm.$^{-1}$, which has not been interpreted. The oxime of this acid also possesses absorption bands indicative of the carboxyl and hydroxy-groups involved in hydrogen bonding, and a strong band at 1692 cm.$^{-1}$ attributed to the carboxyl group. A strong band at 1620 cm.$^{-1}$ is probably due to the C=N vibration, but the broad weak band shown by the parent acid is absent from the oxime.

Summarising the above evidence, it seems to us that the second double bond must be in ring B, and we believe that this double bond is that associated with the lactone ring of ψ-santonin. There are, therefore, three possible positions available for an ethylenic link, namely at C_6–C_7, C_7–C_8, and C_8–C_{11}. A double bond at either C_8–C_9 or at C_9–C_{10} would be part of an enolic system and would not be expected to behave as an olefine. A double bond at C_8–C_{11} is contra-indicated by its ready hydrogenation (cf. Cocker and Hornsby, *J.*, 1947, 1157). Since the conditions for the formation of ψ-santonic acid are mild, it is probable that the second double bond is that associated with the lactone ring in ψ-santonin which is hydrogenolysed on treatment with palladised charcoal in hydrogen. Its position at C_7–C_8 is, therefore, favoured.

In view of the above data we tentatively suggest that ψ-santonic acid is a di-unsaturated γ-hydroxy-acid of structure (I). Confirmation of this view must await the results of oxidation experiments now in hand. If ψ-santonic acid were (II), the light absorption requirements would be satisfied, but the empirical formula, $C_{15}H_{18}O_4,H_2O$, is unlikely; on this basis, ψ-santonin should have the empirical formula, $C_{15}H_{18}O_4$, and possess two double bonds for which there is no evidence.

(I.) 



(II.)

When ψ-santonic acid is treated for extended periods with sodium hydroxide, it yields a *compound*, $C_{15}H_{20}O_4$, possessing a carboxyl group, which has not been further investigated, but, since during this alkaline treatment the specific rotation rises from +65° to +141° [an increase which is paralleled by the increase in rotation when (+)-β-desmotropo-ψ-santonin is epimerised by alkali to (+)-α-desmotropo-ψ-santonin (Cocker, Cross, and Lipman, *loc. cit.*)], it seems reasonable to assume that epimeric change at C_{11} has taken place. The new acid may not have been optically pure, since crystallisation to constant m. p. was very wasteful and the final material was only obtained in small yields. It should be noted that this acid is apparently unhydrated.

Both the anhydrous and the hydrated tetrahydro-ψ-santonic acid undergo lactonisation on heating with acetic anhydride, yielding *α-anhydrotetrahydro-ψ-santonic acid*, $C_{15}H_{22}O_3$, m. p. 147—148°. When heated above their melting points, the tetrahydro-ψ-santonic acids yield *β-anhydrotetrahydro-ψ-santonic acid*, m. p. 159—160°. Both forms are lævorotatory, and the α-form is converted into the β-form on shaking with hydrogen in presence of palladised charcoal. There is, however, no hydrogen uptake. Neither of the anhydro-compounds is identical with tetrahydroanhydro-ψ-santonic acid which is dextrorotatory. β-Anhydrotetrahydro-ψ-santonic acid is not identical with anhydrodihydro-ψ-santonin (Clemo and Cocker, *loc. cit.*). They possess identical melting points, which are, however, depressed on admixture, and have widely differing specific rotations

Infra-red light absorption data show that α- and β-anhydrotetrahydro-ψ-santonic acids and tetrahydroanhydro-ψ-santonic acid are structurally identical. Each has a strong band at 1698 cm.$^{-1}$ indicative of a ketonic group, and another at 1777 cm.$^{-1}$ indicative of a saturated lactone. Bands at 1622 cm.$^{-1}$ and at 832 cm.$^{-1}$, indicative of a double bond, are difficult to

explain. Very weak bands at 3550 and 3380 cm.$^{-1}$, shown by all the lactones mentioned, may be overtones of those at 1777 and 1698 cm.$^{-1}$.

The inter-relations of these anhydro-compounds constitute an interesting stereochemical problem which will be investigated later, but it seems probable that these lactones differ in configuration at C_8 and C_9, the configuration at C_{11} being alike in each case. It is unfortunate that the only lævorotatory compounds so far obtained in the ψ-santonic acid series are saturated, since conversion into the yet unknown lævorotatory desmotropo-ψ-santonins is thus impossible (compare Cocker, Cross, and Lipman, *loc. cit.*).

When either α- or β-anhydrotetrahydro-ψ-santonic acid is hydrolysed, inversion of sign of rotation takes place, and a new mono-hydrated acid is obtained. It is possible that inversion at C_{11} takes place in the alkaline environment. However, when methyl tetrahydro-ψ-santonate is hydrolysed, no similar inversion of sign takes place.

It is significant that the various acids described have all been isolated in a hydrated form, whilst the lactones and ester described have been obtained only anhydrous, with the exception of the epoxide of ψ-santonic acid during the formation of which lactonisation takes place. It would appear, therefore, that in general it is the free carboxyl group which is hydrated. The infra-red data confirm that hydrogen bonding is present in the acids, but the significance of it is not clear to us.

Experimental.

ψ-Santonic Acid, $[\alpha]_D^{16°}$ +65·4° (*c*, 1·1 in alcohol) (cf. Clemo and Cocker, *J.*, 1946, 35, who gave $[\alpha]_D^{20°}$ +25·2°), can also be obtained (2 g.) by stirring ψ-santonin (3 g.) for 2—3 hours with sulphuric acid (5 c.c.) and water (10 c.c.), or by shaking ψ-santonin for 24 hours with 20% hydrochloric acid. By treatment with concentrated hydrochloric acid for 12 hours, ψ-santonin yields also a *chloro*-compound which crystallises from dilute acetic acid as prisms, m. p. 289—290° (Found: C, 56·2; H, 6·9. $C_{15}H_{23}O_5Cl$ requires C, 56·6; H, 7·2%). *ψ-Santonic acid* 2 : 4-*dinitrophenylhydrazone* has m. p. 193—194° (Found: C, 55·0; H, 5·6. $C_{21}H_{26}O_8N_4$ requires C, 54·5; H, 5·6%). *Anhydro-ψ-santonic acid phenylhydrazone*, formed with phenylhydrazine in boiling acetic acid, separated from benzene in small orange needles, m. p. 160° (Found: C, 75·2; H, 7·0. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·1%).

ψ-Santonic Acid Diepoxide.—ψ-Santonic acid (1 g.) in chloroform (50 c.c.) was set aside for 15 days at 0° with perbenzoic acid in chloroform (20 c.c.; 0·9N.). The solid *diepoxide* produced was washed with chloroform and then crystallised from alcohol in prisms, m. p. 265—266° after softening at 252°, $[\alpha]_D^{19°}$ −45·9° (*c*, 0·25 in alcohol) (Found: C, 60·7; H, 6·7. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%). In a quantitative experiment 1·8 double bonds per mol. were found.

Condensation of ψ-Santonic Acid with o-*Aminobenzaldehyde.*—This was performed as described for ψ-santonin (*loc. cit.*). The gummy *product* which was first obtained gave a solid, m. p. 138—140°, on rubbing with light petroleum (Found: N, 3·5. $C_{22}H_{25}O_4N$ requires N, 3·8%).

Tetrahydro-ψ-santonic Acid (III).—ψ-Santonic acid (1 g.) in acetic acid (25 c.c.) was shaken in hydrogen for 11 hours with palladised charcoal (0·1 g.). The *tetrahydro-acid* separated from dilute alcohol in needles (0·4 g.), m. p. 197—198°, $[\alpha]_D^{23°}$ +52° (*c*, 0·9 in alcohol) (Found: C, 67·1; H, 8·9. $C_{15}H_{24}O_4$ requires C, 67·1; H, 8·9%). In a quantitative experiment two double bonds per mol. were found. The *oxime* (needles from alcohol) had m. p. 230° (decomp.) (Found: C, 63·8; H, 8·8. $C_{15}H_{25}O_4N$ requires C, 63·6; H, 8·8%). A *monohydrate* consisted of prisms, m. p. 190—191°, $[\alpha]_D^{14°}$ +32·4° (*c*, 0·9 in alcohol) (Found: C, 63·3; H, 9·0. $C_{15}H_{24}O_4,H_2O$ requires C, 62·9; H, 9·0%).

Methyl tetrahydro-ψ-santonate (IV) was obtained when the acid (III) (0·2 g.) was heated under reflux in methyl alcohol with methyl iodide (4 c.c.) and anhydrous potassium carbonate (1·0 g.). The *ester* separated from light petroleum (b. p. 60—80°) in needles (50 mg.), m. p. 68—69° (Found: C, 68·5; H, 8·7. $C_{16}H_{26}O_4$ requires C, 68·1; H, 9·2%).

Condensation of Tetrahydro-ψ-santonic Acid with o-*Aminobenzaldehyde.*—This gave a *product* which crystallised from alcohol in needles, m. p. 212—213° (Found: C, 74·9; H, 7·4. $C_{22}H_{27}O_3N$ requires C, 74·8; H, 7·6%).

Anhydro-ψ-santonic Acid (V).—ψ-Santonic acid (0·6 g.) was heated at 200° for 10 minutes; after being cooled, the product was agitated with 10% sodium carbonate. The residual *lactone* crystallised from alcohol as pale yellow prisms (0·5 g.), m. p. 191—192°, $[\alpha]_D^{19°}$ +110° (*c*, 1·1 in chloroform) (Found: C, 72·6; H, 7·3. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·3%).

Tetrahydroanhydro-ψ-santonic Acid (VI).—The lactone (V) (0·2 g.) in acetic acid (10 c.c.) was shaken in hydrogen for 9 hours with palladised charcoal (0·3 g.). The resulting gummy product solidified on stirring with alcohol, from which solvent the required *lactone* was obtained (0·1 g.) as needles, m. p. 119—120°, $[\alpha]_D^{19°}$ +10·2° (*c*, 1·0 in alcohol) (Found: C, 71·9; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). In a quantitative experiment, 4 atoms of hydrogen per molecule were absorbed. The 2 : 4-*dinitrophenylhydrazone* of *tetrahydroanhydro-ψ-santonic acid* separated from alcohol as orange needles, m. p. 220—221° (decomp.) (Found: C, 58·5; H, 5·9. $C_{21}H_{26}O_6N_4$ requires C, 58·6; H, 6·0%).

Hexahydroanhydro-ψ-santonic Acid (VII).—Anhydro-ψ-santonic acid (V) (0·5 g.) in acetic acid (15 c.c.) was shaken in hydrogen for 20 hours with platinic oxide (0·1 g.). The *lactone* produced crystallised from dilute alcohol as long needles (0·1 g.), m. p. 150—152° (Found: C, 71·9; H, 8·7. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%). In a quantitative experiment 6 atoms of hydrogen per molecule were absorbed.

Hexahydro-ψ-santonic Acid.—ψ-Santonic acid (1·0 g.) in glacial acetic acid (15 c.c.), when shaken with platinic oxide (0·5 g.) in an atmosphere of hydrogen for 12 hours, gave the *hexahydro-acid*, which crystallised from dilute alcohol as long, glistening needles, m. p. 185° (Found: C, 63·7; H, 9·4. $C_{15}H_{26}O_4,H_2O$ requires C, 62·5; H, 9·6%). Its *acetate*, first obtained as a gum, eventually solidified and

crystallised from dilute alcohol as needles, m. p. 120—121° (Found : C, 69·2; H, 8·4. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·6%). This compound was a lactone. In a quantitative experiment, 5·4 atoms of hydrogen per molecule were absorbed.

α-Anhydrotetrahydro-ψ-santonic Acid.—When tetrahydro-ψ-santonic acid, m. p. 197—198°, was heated with a mixture of acetic anhydride and sodium acetate, it yielded solid ***α-anhydrotetrahydro-ψ-santonic acid***, which crystallised from dilute acetic acid as needles, m. p. 147—148°, $[\alpha]_D^{21°}$ −133°, (*c*, 0·4 in alcohol) (Found : C, 72·3, 72·4; H, 8·2, 8·5. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as orange needles, m. p. 210° (decomp.) (Found : C, 58·3; H, 6·0. $C_{21}H_{26}O_6N_4$ requires C, 58·5; H, 6·0%). This anhydro-acid (0·2 g.) was shaken in acetic acid (10 c.c.) with palladised charcoal (0·1 g.) in hydrogen. Crystallisation of the product from dilute alcohol yielded colourless needles (0·1 g.), m. p. 159—160°, $[\alpha]_D^{20°}$ −37·5° (c, 0·4 in alcohol) (Found : C, 72·0; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%), identical with ***β-anhydrotetrahydro-ψ-santonic acid*** (0·1 g.; m. p. 159—160°. Found : C, 71·8; H, 8·8%) obtained when tetrahydro-ψ-santonic acid (0·2 g.) was heated at 195—200° for 10 minutes.

Hydrolysis of α- and β-Anhydrotetrahydro-ψ-santonic Acid.—α-Anhydrotetrahydro-ψ-santonic acid (0·06 g.) was heated with 2N-sodium hydroxide (4 c.c.) until complete solution was effected. The cooled solution was acidified at 0° with concentrated hydrochloric acid. The resultant *acid* crystallised from dilute alcohol as long, silky needles, m. p. 205—206°, $[\alpha]_D^{19°}$ +103·3° (*c*, 0·272 in alcohol) (Found : C, 62·9; H, 8·9. $C_{15}H_{24}O_4,H_2O$ requires C, 62·9; H, 9·1%). It dissolved in sodium carbonate solution with effervescence. β-Anhydrotetrahydro-ψ-santonic acid yielded the same acid.

Action of Sodium Hydroxide on ψ-Santonic Acid.—ψ-Santonic acid (0·7 g.) in sodium hydroxide (6 c.c., 8%) was set aside at room temperature for one week. The filtered solution was acidified and gave a solid (0·55 g.), m. p. 218—220°. After many crystallisations from dilute acetic acid, the *acid* was deposited as minute needles, m. p. 254°, $[\alpha]_D^{13°}$ +141° (*c*, 0·8 in acetic acid) (Found : C, 67·2; H, 7·7; equiv., 250. $C_{15}H_{20}O_4$ requires C, 67·4; H, 8·0%; equiv., 264).

Deoxytetrahydro-ψ-santonic Acid.—The tetrahydro-compound (III) (2·8 g.) was heated under reflux with amalgamated zinc (15 g.), concentrated hydrochloric acid (30 c.c.), and toluene (30 c.c.) for 24 hours. On being rubbed with ether, the glassy product gave a white solid (0·35 g.), which crystallised from dilute alcohol as long needles, m. p. 166—167°, $[\alpha]_D^{18°}$ −37·3° (*c*, 0·92 in chloroform) (Found : C, 72·1; H, 8·4. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). This *compound* has not been further investigated. Its 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as yellow needles, m. p. 234—235° (Found : C, 58·0; H, 5·9. $C_{21}H_{26}O_6N_4$ requires C, 58·1; H, 6·0%). The gummy residue from the white solid was heated at 280—340° for 40 hours with an excess of selenium (1 g.), yielding an oil (0·2 g.) which was distilled from sodium, b. p. 110—115°/2—3 mm. Its picrate crystallised from alcohol as orange needles, m. p. 91—92°, which did not depress the m. p. of the picrate of authentic 1-methyl-7-ethylnaphthalene, m. p. 94° (Ruzicka and Eichenberger, *Helv. Chim. Acta*, 1930, **13**, 117).

Epoxide of ψ-Santonin. Titration of ψ-Santonin with Perbenzoic Acid.—ψ-Santonin (1·001 g.) in chloroform (10 c.c.) was set aside at 0° for 15 days with a solution of perbenzoic acid (20 c.c.; 0·9N.). Titration of the excess of perbenzoic acid in an aliquot proportion showed the presence of one double bond per molecule. The remaining solution was washed with sodium bicarbonate and evaporated to dryness; a gum was obtained which solidified on grinding with ether. The *epoxide* (0·85 g., m. p. 135°) crystallised from a mixture of ethyl acetate and light petroleum as rosettes of needles, m. p. 145·5—146·5° (Found : C, 64·4; H, 7·2. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·1%). It yielded a 2 : 4-dinitrophenylhydrazone, m. p. 238—240°.

Grateful acknowledgment is made of grants from Messrs. T. and H. Smith, Ltd., Imperial Chemical Industries, Ltd., and the Medical Research Council of Ireland. The authors are indebted to Imperial Chemical Industries, Ltd. (Billingham Division) for the infra-red data, and to the Royal Dublin Society for the loan of a polarimeter.

TRINITY COLLEGE, DUBLIN. [*Received, October 22nd*, 1948.]

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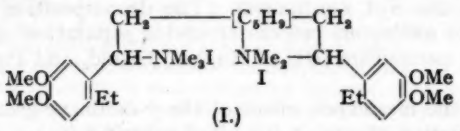
254. *Studies on the Structure of Emetine. Part III. Stability of Some α-Arylalkyl-trimethylammonium Iodides.*

By GEOFFREY NORCROSS and H. T. OPENSHAW.

In view of the instability of *N*-methylemetinetetrahydromethine dimethiodide (I), the behaviour of a number of model methiodides containing the α-alkylbenzylamine structure has been studied. Ready decomposition with fission to yield trimethylamine hydriodide occurs only when a methoxy-group is present in the *p*-position of the benzene ring, and is further facilitated by alkylation of the β-carbon atom of the side-chain. These results accord with current theories of the mechanisms of such elimination reactions. In contrast, 2-*p*-methoxyphenyl-1-methylpiperidine methiodide (VII), in which the nitrogen atom is cyclically linked, is stable at 100°.

THE decomposition of *N*-methylemetinetetrahydromethine dimethiodide (I), in solution at 100°, to give trimethylamine hydriodide and an unsaturated monomethiodide (II), represents an unusual type of Hofmann degradation. By analogy with the similar reactions of the methiodides of gramine and of pavinemethine, the decomposition has been ascribed to the presence in (I) of a suitably substituted benzylamine structure (Battersby and Openshaw,

Part I, this vol., p. S 59). In order to determine more fully the structural features required, a qualitative study has been made of the stability of some α-arylalkyl-trimethylammonium iodides.



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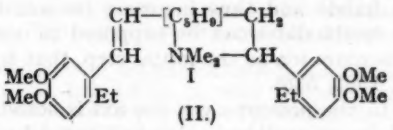

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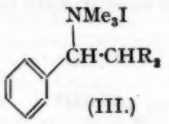

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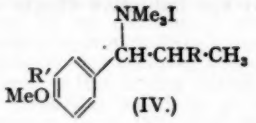

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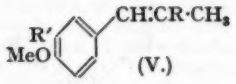

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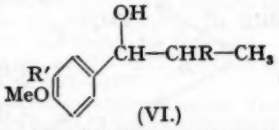

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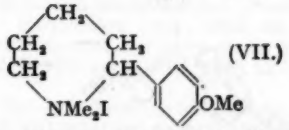


(VII.)

Trimethyl-1-*phenylethylammonium iodide* (III; R = H) and *trimethyl*-1-*phenylisobutylammonium iodide* (III; R = Me) were unaffected by prolonged heating in aqueous solution at 100°. On similar treatment, *trimethyl*-1-3′ : 4′-*dimethoxyphenyl*-n-*propylammonium iodide* (IV; R = H, R′ = OMe) underwent slow decomposition with the formation of trimethylamine hydriodide and a neutral, water-insoluble oil. The yield of the latter was *ca.* 13% after 10 hours and *ca.* 70% after 48 hours, and this oil appeared to be a mixture of *O*-methyl*iso*eugenol (V; R = H, R′ = OMe) and α-3 : 4-dimethoxyphenyl-*n*-propyl alcohol (VI; R = H, R′ = OMe); after treatment of a specimen with dilute acid, the known dimer of *O*-methyl*iso*eugenol was obtained. *Trimethyl*-1-p-*methoxyphenylisobutyl*- (IV; R = Me, R′ = H) and -1-3 : 4-*dimethoxyphenylisobutylammonium iodides* (IV; R = Me, R′ = OMe) were very much less stable, decomposition being virtually complete after one hour at 100°. The crystalline, neutral product obtained from the latter salt was shown to be 1-3′ : 4′-*dimethoxyphenylisobutyl alcohol* (VI; R = Me, R′ = OMe) by comparison with a specimen synthesised from veratraldehyde and *iso*propylmagnesium bromide. The neutral product from (IV; R = Me, R′ = H) was an oil, which gave a rather unsatisfactory analysis for the corresponding alcohol, but comparison with the behaviour of a synthetic specimen indicated it to be essentially 1-*p*-methoxyphenyl-*iso*butyl alcohol (VI; R = Me, R′ = H). Decomposition of (IV; R = Me, R′ = OMe) in diethyl ketone solution at 100°, however, proceeded in a manner analogous to that of (I) under similar conditions, giving trimethylamine hydriodide and the unsaturated compound 1-3′ : 4′-*dimethoxyphenylisobut*-1-*ene* (V; R = Me, R′ = OMe).

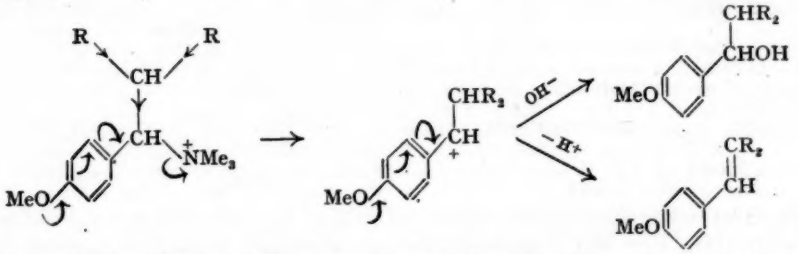
The methiodides used in this investigation were prepared by treatment of the corresponding primary amines with methyl iodide and aqueous sodium carbonate at 45°. In order to avoid possible decomposition of the methiodides during their preparation, an alternative method was investigated, in which the primary amines were methylated by formaldehyde and formic acid (Icke, Wisegarver, and Alles, *Org. Synth.*, 1945, **25**, 89) and the resulting tertiary amines treated with methyl iodide in ethereal solution at room temperature. Although 1-phenyl-*iso*butylamine was satisfactorily converted into its *NN*-dimethyl derivative, 1-p-*methoxyphenylisobutylamine* gave none of the desired tertiary amine, but largely decomposed to trimethylamine and an unsaturated, neutral oil which had a powerful odour of aniseed and appeared to be impure β-methylanethole (V; R = Me, R′ = H). Similar treatment of 1-3′ : 4′-*dimethoxyphenylisobutylamine* gave a 30% yield of the *NN*-dimethyl derivative together with a considerable amount of 1-3′ : 4′-dimethoxyphenyl*iso*butyl alcohol. Thus, on heating with formaldehyde and formic acid these amines undergo a decomposition similar to that shown by their methiodides.

The thermal decomposition of the dimethiodide (I) involves only one of the two quaternary nitrogen atoms present, although both are linked to 3 : 4-dimethoxybenzyl groups. The environment of the stable nitrogen atom differs mainly in that this atom forms part of a ring. In order to determine the influence of such a structure on the stability, 2-*p*-methoxyphenylpiperidine was converted into its *methiodide* (VII). This substance proved to be completely stable in aqueous solution at 100°.

From the experimental results obtained, it is clear that the decomposition of the quaternary iodides is induced by the presence of a methoxy-group in the *p*-position of the benzene ring

and assisted by alkylation of the β-carbon atom. The effect can be correlated with the influence of a *p*-methoxy-group on the ease of hydrolysis of the benzyl halides (Lapworth and Shoesmith, *J.*, **1922**, **121**, 1391). In the latter case, the methoxy-group facilitates the ionisation of the halide and thus increases its reactivity by the S_N1 mechanism. The decomposition of the methiodides can be supposed to occur by an analogous process involving separation of a carbonium ion as the initial step, that is, by the mechanism (*B*1) of Hughes, Ingold, and Patel (*J.*, **1933**, 526).

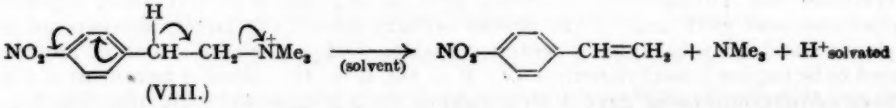
In the present case, the ion is stabilised by the mesomeric effect of the *p*-methoxy-group, and its separation is also facilitated by the inductive effects of the alkyl substituents on the β-carbon atom.



In the second stage the ion either loses a proton from the β-carbon atom, to give an unsaturated product, or combines with an anion. In aqueous solution, the substances described in this paper appear to follow principally the latter course, a hydroxyl ion being taken up to produce an alcohol. In diethyl ketone, the principal reaction is probably loss of a proton, but the liberation of iodine which occurred when the crude reaction product from (IV; R = Me, R′ = OMe) was distilled suggested that some of the unstable benzyl iodide was also produced by interaction of the carbonium ion with iodide ion. Although no alcohol was isolated from the decomposition of (I) in aqueous solution, such a substance may be formed to some extent, since the yield of pure product is much lower than results from its decomposition in diethyl ketone.

The stability of the cyclic compound (VII) may perhaps be ascribed to the reversibility of the C–N fission process. In the case of an open-chain compound, it is possible for the two fission products to separate quickly to a distance sufficient to prevent recombination, but with the cyclic compound such rapid separation of the carbonium ion and the nitrogen atom may be prevented by the restraint of the carbon chain connecting them.

The instability of the methiodides described in this paper provides an interesting comparison with the instability of trimethyl-*p*-nitrophenylethylammonium iodide (VIII) (Hughes and Ingold, *J.*, 1933, 523). This compound also decomposes in aqueous solution at 100° to give trimethylamine hydriodide and the unsaturated substance, *p*-nitrostyrene, but the decomposition proceeds by an entirely different mechanism [mechanism (*A*1) of Hughes, Ingold, and Patel, *loc. cit.*] which is initiated by the tendency to ionisation of a hydrogen atom attached to the β-carbon atom. Such an ionisation is facilitated by polarisation effects exactly opposite to those which cause the instability of the methiodides we have described, the two reactions standing at opposite ends of the " mechanistic series ".



(VIII.)

Independently of our work (Part I, *loc. cit.*), Späth and Pailer (*Monatsh.*, 1948, **78**, 348) also observed that *N*-methylemetinetetrahydromethine is converted into (II) and trimethylamine hydriodide when heated with methyl iodide in methanol. Since the work described in our present paper was completed, Pailer and Bilek (*ibid.*, 1948, **79**, 135) have described a similar degradation of two synthetic dimethyl-1-3′ : 4′-dimethoxy-6′-ethylphenylalkylamines.

Experimental.

(All m. p.s are corrected.)

Trimethyl-1-phenylethylammonium Iodide (III; R = H).—A mixture of 1-phenylethylamine (3·5 g.), methyl iodide (28 g.) and aqueous sodium carbonate (6 g. in 40 ml.) was warmed under reflux on the water-bath for 7 hours. After evaporation of excess of methyl iodide, the cooled solution was extracted

thrice with chloroform. The extract was dried (K_2CO_3) and evaporated, leaving a residue which crystallised on trituration with ether. On crystallisation from anhydrous alcohol, the *methiodide* formed deliquescent, colourless plates (4·65 g., 55·2%), which after recrystallisation had m. p. 144·5—145·5° (Found: N, 4·8; I, 43·5. $C_{11}H_{18}NI$ requires N, 4·8; I, 43·6%). A solution of the methiodide (1·07 g.) in water (30 ml.) was boiled under reflux for 6 hours. There was no evidence of decomposition, and the methiodide was recovered unchanged.

1-*Phenylisobutylamine.*—*iso*Butyrophenone (71 g.) was treated with anhydrous ammonium formate (100 g.) essentially as described by Ingersoll (*Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 503); a final reaction temperature of 200—210° was employed. Hydrolysis of the crude formamide with boiling hydrochloric acid was continued for 1½ hours, and on cooling the solution deposited crystals of the amine hydrochloride which were redissolved by the addition of water. The aqueous solution was washed with benzene, made alkaline with sodium hydroxide (65 g.), and steam-distilled, the distillate separating into two layers. The upper layer of amine was removed and the aqueous layer extracted with benzene, the extract being added to the amine. After drying (KOH) and distillation, 1-phenyl*iso*butylamine (54·7 g., 77%), was obtained as a colourless liquid, b. p. 102—104°/20 mm. The neutral oxalate separated as rosettes of colourless needles, m. p. 177—178°, from anhydrous alcohol [Found: C, 68·0; H, 8·1. Calc. for $(C_{10}H_{15}N)_2,C_2H_2O_4$: C, 68·0; H, 8·3%]; Konowalow (*Ber.*, 1895, **28**, 1852) gives m. p. 120·5—122° (decomp.) for this salt. The hydrochloride crystallised from water in colourless, prismatic needles, m. p. 276—277°; Billon (*Ann. Chim.*, 1927, **7**, 314) gives m. p. 275°, and Konowalow (*loc. cit.*) gives m. p. 275—277°.

Trimethyl-1-*phenylisobutylammonium Iodide* (III; R = Me).—1-Phenyl*iso*butylamine (6 g.) was heated under reflux for 13 hours with methyl iodide (32 g.) and aqueous sodium carbonate (8 g. in 50 ml.), and the product isolated as described above. The *methiodide* (5·39 g., 42%) formed needles, m. p. 147·5—148·5°, from alcohol–ether (Found: I, 39·9. $C_{13}H_{22}NI$ requires I, 39·8%). No decomposition occurred when an aqueous solution of the methiodide was boiled under reflux for 10 hours.

1-3′ : 4′-*Dimethoxyphenyl*-n-*propylamine.*—This amine was prepared from propioveratrone (17·5 g.) (Adams, Geissman, Baker, and Teeter, *J. Amer. Chem. Soc.*, 1941, **63**, 528) and ammonium formate (18 g.) essentially as described above for 1-phenyl*iso*butylamine. It was obtained as a colourless liquid (5·2 g., 30%), b. p. 120°/0·2 mm., and formed a *picrate*, rosettes of yellow needles, m. p. 182—183°, from alcohol (Found: C, 48·1; H, 4·8; N, 12·9. $C_{11}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 48·1; H, 4·7; N, 13·2%).

Trimethyl-1-3′ : 4′-*dimethoxyphenyl*-n-*propylammonium Iodide* (IV; R = H, R′ = OMe).—A mixture of the above amine (2·51 g.), methyl iodide (9·5 g.), and aqueous sodium carbonate (3 g. in 45 ml.) was heated gently for ½ hour, and the colourless, flocculent precipitate was collected. On crystallisation from anhydrous alcohol, the *methiodide* formed colourless, lozenge-shaped plates, m. p. *ca.* 258° (decomp.) after sintering from 204° (Found: C, 46·2; H, 6·4; N, 4·2. $C_{14}H_{24}O_2NI$ requires C, 46·0; H, 6·6; N, 3·8%).

Thermal Decomposition of the Methiodide (IV; R = H, R′ = OMe).—(*a*) A solution of the methiodide (1·16 g.) in water (25 ml.) was boiled under reflux for 10 hours. Extraction of the cooled, turbid solution with ether gave an oil (0·14 g.), which was redissolved in ether and shaken with dilute (1 : 1) hydrochloric acid (5 ml.). Evaporation of the solvent left an oil (0·075 g.) which rapidly solidified. Crystallisation from light petroleum gave bis-*O*-methyl*iso*eugenol, m. p. 104—106·5° (Szeki, *Ber.*, 1906, **39**, 2422, gives m. p. 106°), which did not react with bromine in carbon tetrachloride (Found: C, 74·1; H, 8·0; OMe, 34·7. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9; OMe, 34·8%). Evaporation of the aqueous liquor left a pale brown solid (0·87 g.), which liberated trimethylamine (picrate, m. p. 217°) on treatment with alkali.

(*b*) A solution of the methiodide (1·895 g.) in water (25 ml.) was boiled under reflux for 48 hours. Extraction with ether gave a light brown, viscous oil (0·709 g., *ca.* 70%). After distillation at 9 mm. from a bath at 150°, the material analysed as a mixture of *O*-methyl*iso*eugenol and 1-3′ : 4′-dimethoxyphenyl-*n*-propyl alcohol (Found: C, 69·9; H, 8·2; OMe, 32·4. Calc. for $C_{11}H_{14}O_2$: C, 74·1; H, 7·9; OMe, 34·9. Calc. for $C_{11}H_{16}O_3$: C, 67·3; H, 8·2; OMe, 31·7%). It decolorised bromine in carbon tetrachloride solution. [Interaction of ethylmagnesium bromide and veratraldehyde gave a product which after distillation at 10^{-3} mm., consisted of a similar mixture of the alcohol and *O*-methyl*iso*eugenol, containing about 30% of the latter as shown by bromine titration (cf. Béhal and Tiffeneau, *Bull. Soc. chim.*, 1908, [iv], **3**, 309; Müller, Raltschewa, and Papp, *Ber.*, 1942, **75**, 700).] The aqueous liquor remaining after the ether extraction contained trimethylamine hydriodide and a little unchanged methiodide.

p-*Methoxyisobutyrophenone.*—Prepared by a method similar to that used for propioveratrone (Adams *et al.*, *loc. cit.*), this ketone distilled at 82—87°/4 × 10^{-2} mm. as a colourless oil, giving a semicarbazone in felted needles, m. p. 183·5—184·5°, from methyl alcohol (Found: C, 61·2; H, 7·0. Calc. for $C_{12}H_{17}O_2N_3$: C, 61·2; H, 7·3%). Tiffeneau and Levy (*Bull. Soc. chim.*, 1926, [iv], **39**, 763) claim to have prepared this ketone, but give the m. p. of the semicarbazone as 212—213°. Sosa (*Ann. Chim.*, 1940, **14**, 5) gives m. p. 193—194° (block) and 205—206° (capillary).

Trimethyl-1-p-*methoxyphenylisobutylammonium Iodide* (IV; R = Me, R′ = H).—*p*-Methoxy*iso*butyrophenone (14·3 g.) was treated with ammonium formate (16·3 g.) as described above. The amine (7·1 g., 50%) was a colourless liquid, b. p. 83°/0·1 mm., and formed a *picrate* which crystallised from alcohol as yellow prisms, which melted at 183·5—184°, immediately resolidified, and then melted with decomposition at 271—273° (Found: N, 13·5. $C_{11}H_{17}ON,C_6H_3O_7N_3$ requires N, 13·7%). The amine (1·2 g.) was treated with aqueous sodium carbonate (1·5 g. in 25 ml.) and boiling methyl iodide (9·5 g.) for 30 minutes. When the mixture had been kept in the cold, *trimethyl*-1-p-*methoxyphenylisobutylammonium iodide* (1·83 g., 78%) separated as a white, flocculent precipitate. It was purified by shaking it with cold anhydrous alcohol for 5 hours and concentrating the filtered and seeded solution by evaporation in a partly evacuated desiccator over calcium chloride; it formed octahedra which began to decompose at *ca.* 165° and finally melted at 269—271° (Found: C, 48·3; H, 7·1; N, 3·9. $C_{14}H_{24}ONI$ requires C, 48·15; H, 6·9; N, 4·0%).

Thermal Decomposition of the Methiodide (IV; R = Me, R′ = H).—A solution of the methiodide (1·043 g.) in water (100 ml.) was shaken with peroxide-free ether to ensure the absence of ether-soluble materials, separated, and boiled under reflux. A steam-volatile oil appeared in the condensate after 5 minutes. After 40 minutes the solution was cooled and extracted with ether, giving a colourless, odourless oil (0·348 g.) which did not react with bromine in carbon tetrachloride; this distilled at 0·5 mm. from a bath at 90°, but gave unsatisfactory analytical results (Found : C, 72·6; H, 8·6. Calc. for $C_{11}H_{16}O_2$: C, 73·3; H, 8·9%). When boiled under atmospheric pressure, it developed a strong aniseed odour and became unsaturated.

Anisaldehyde was treated with *iso*propylmagnesium bromide in the usual manner, and the intermediate complex decomposed with ice and ammonium chloride (Sosa, *loc. cit.*). After removal of unchanged anisaldehyde with sodium bisulphite, a light brown oil (21% yield) was obtained, which did not smell of aniseed. Bromine titration indicated the presence of about 5% of the related unsaturated compound. The substance distilled at 125—140°/16 mm., and the distillate contained 54% of unsaturated material and had a strong odour of aniseed. Perkin (*J.*, 1879, **35**, 145) describes β-methylanethole (V; R = Me, R′ = H) as possessing an odour of aniseed.

iso*Butyroveratrone.*—A solution of *iso*butyryl chloride (31 g.) in pure benzene (50 ml.) was added during 1½ hours to a cooled and stirred mixture of veratrole (25 g.), aluminium chloride (28 g.), and benzene (100 ml.). The mixture was heated under reflux for 1 hour with stirring and decomposed in the usual manner. The benzene solution of the product was shaken with aqueous sodium hydroxide, and the phenolic material thus extracted was remethylated by shaking the alkaline solution with methyl sulphate and extracting it with benzene. The combined benzene solutions were distilled through a short column. *iso*Butyroveratrone (32·1 g., 85%) was obtained as a colourless liquid, b. p. 116—117°/0·2 mm. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in short, orange needles, m. p. 189—189·5° (Found : C, 55·9; H, 5·3; N, 14·4. $C_{18}H_{20}O_8N_4$ requires C, 55·7; H, 5·2; N, 14·4%). The *semicarbazone* formed colourless, rectangular tablets, m. p. 149—150°, from methyl alcohol (Found : N, 15·6. $C_{13}H_{19}O_2N_3$ requires N, 15·9%).

Trimethyl-1-3′ : 4′-*dimethoxyphenyliso*butylammonium *Iodide* (IV; R = Me, R′ = OMe).—The foregoing ketone (31·2 g.) was treated with ammonium formate (32·3 g.) in the usual manner. 1-3′ : 4′-Dimethoxyphenyl*iso*butylamine (23·5 g., 75%) distilled at 101—105°/0·2 mm. as a colourless oil, and formed a *picrate*, yellow plates (from alcohol), which melted on rapid heating at 188·5—190·5°, and on slow heating at 255° (decomp.) after softening at 175° (Found : C, 49·7; H, 5·1; N, 13·0. $C_{12}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 49·3; H, 5·1; N, 12·8%). The amine (5 g.) was methylated in the usual manner for 1 hour. Excess of methyl iodide was removed by distillation, and the aqueous solution was extracted twice with ether to remove a little water-insoluble material. The *methiodide* was isolated by extraction with chloroform. It crystallised in contact with alcohol as colourless plates (6·4 g., 95%). The salt was recrystallised by evaporating its cold solution in anhydrous alcohol under reduced pressure; when rapidly heated, it had m. p. 214—215° (decomp.) (Found : C, 46·8; H, 6·7; N, 4·2; OMe, 16·4. $C_{15}H_{26}O_2NI$ requires C, 47·5; H, 6·9; N, 3·7; OMe, 16·35%). Repeated crystallisation from hot alcohol caused almost complete decomposition to yield trimethylamine hydriodide, m. p. 253—256° (decomp.) (Found : C, 20·0; H, 5·6; N, 7·4. Calc. for $C_3H_{10}NI$: C, 19·2; H, 5·4; N, 7·5%).

Thermal Decomposition of the Methiodide (IV; R = Me, R′ = OMe).—(a) *In water.* A solution of the methiodide (0·57 g.) in water (30 ml.) was boiled under reflux. After 3 minutes the condensate became milky and an oil separated from the solution. After 1 hour the solution was cooled and extracted with ether, yielding, after evaporation of the ether, a brown oil which largely solidified on standing. Crystallisation from water and from light petroleum gave long, colourless needles of 1-3′ : 4′-*dimethoxyphenyliso*butyl *alcohol*, m. p. 66—67° (Found : C, 69·0; H, 8·6. $C_{12}H_{18}O_3$ requires C, 68·6; H, 8·6%). Trimethylamine was liberated when the aqueous solution from the decomposition was made alkaline, and was identified as the picrate, m. p. 215°.

(b) *In diethyl ketone.* The methiodide (3 g.) was suspended in diethyl ketone (50 ml.), and the mixture heated at 100° under reflux for 2 hours. There was a noticeable odour of trimethylamine, and the evolved vapours were alkaline to litmus. At no time was a homogeneous solution obtained. The cooled mixture was filtered, and the precipitate (1·37 g.; 93%), which was washed with a little acetone, was identified as trimethylamine hydriodide. The filtrate was evaporated under reduced pressure, and the residue dissolved in peroxide-free ether. A trace of insoluble material (mainly trimethylamine hydriodide) was removed and the solution was evaporated, leaving an orange mobile oil (1·61 g.). Distillation gave a fraction (1·425 g.), b. p. 150—151°/13 mm., which was strongly coloured with iodine. It was dissolved in ether and shaken with sodium thiosulphate solution; the recovered oil had a pale straw colour, and on distillation at 147—148°/10 mm. the first portion of the distillate again contained free iodine, which was removed as before. A third distillation gave 1-3′ : 4′-*dimethoxyphenyliso*but-1-*ene* (0·74 g.) as a colourles,s liquid $n_D^{17°}$ 1·5565 (Found : C, 75·0; H, 8·4. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%).

Synthesis of 1-3′ : 4′-*Dimethoxyphenyliso*butyl *Alcohol* (VI; R = Me, R′ = OMe).—A solution of veratraldehyde (16·45 g.) in anhydrous ether (30 ml.) was added during 30 minutes to the Grignard reagent prepared from *iso*propyl bromide (15·5 g.), magnesium (3·8 g.), and anhydrous ether (25 ml.). The reaction mixture was decomposed with ice and ammonium chloride, and the ethereal extract of the product was shaken with sodium hydrogen sulphite solution, dried, and evaporated, leaving a brown oil (6·79 g.) which partly crystallised when seeded with the alcohol (VI; R = Me, R′ = OMe). The crystalline material was separated from the oil by filtration, and after crystallisation from light petroleum formed colourless needles, m. p. 65·5—67° (undepressed on admixture with the material obtained from decomposition of the methiodide). The filtered oil distilled at 151—152°/15 mm., the distillate being colourless and having $n_D^{17°}$ 1·5565. It immediately decolorised a solution of bromine in carbon tetrachloride.

Methylation of 1-3′ : 4′-*Dimethoxy- and* 1-p-*Methoxy-phenyliso*butylamine.—A mixture of 1-3 : 4-dimethoxyphenyl*iso*butylamine (7·16 g.), 85% formic acid (15 ml.), and paraformaldehyde (4·1 g.) was

heated under reflux in an oil bath at 120—140°. After a few hours, an oil was seen floating on the aqueous solution. After 17 hours, the cooled mixture was acidified (Congo-red) with hydrochloric acid and extracted with ether. Evaporation of the aqueous solution under reduced pressure left a white solid together with a little brown oil; the latter was removed by washing with ether, the washings being added to the ethereal extract. The solid was dissolved in water and treated with sodium hydroxide, whereupon a strong odour of trimethylamine was observed. Ether extraction afforded a brown oil (3·24 g.), which on distillation at 141°/11 mm. gave a colourless liquid (2·43 g., 30%) which crystallised on standing in short, colourless needles, m. p. 18—19°. The product did not react with toluene-*p*-sulphonyl chloride and aqueous sodium hydroxide, and on treatment with ethereal methyl iodide at room temperature was converted into the methiodide, identical with that described above. Evaporation of the original ethereal extract gave a pale brown oil, with an odour of formic acid. After removal of this contaminant by washing with water, the oil partly crystallised when kept. The solid was collected and crystallised from water and then from light petroleum, giving colourless needles, m. p. 66—67°, identified as 1-3′ : 4′-dimethoxyphenyl*iso*butyl alcohol.

Similar treatment of 1-*p*-methoxyphenyl*iso*butylamine (5·9 g.) also gave trimethylamine, together with a small amount of an impure, oily base. The main product (2·4 g.) was a neutral oil, b. p. 130—140°/12 mm., which was unsaturated and had a strong odour of aniseed. Analytical results were unsatisfactory.

2-p-*Methoxyphenylpiperidine*.—A solution of 2-*p*-methoxyphenylpyridine (5·29 g.) (Haworth, Heilbron, and Hey, *J.*, 1940, 360) in anhydrous alcohol (40 ml.) was heated under reflux, and sodium (12·5 g.) was added in portions during 30 minutes. Three additional 20-ml. portions of alcohol were also added at intervals during this process to maintain a vigorous reaction. Finally, unchanged sodium was destroyed by the gradual addition of 50% aqueous alcohol (30 ml.) and then water (10 ml.). Alcohol was removed by evaporation under reduced pressure, the base separating from the residual aqueous solution as an oil which solidified on cooling. It was extracted with ether, and the moist ethereal extract was treated with a slow stream of carbon dioxide for two hours. The white, flocculent precipitate of amine carbonate (4·96 g.) was collected and washed with anhydrous ether. The ethereal filtrate and washings were concentrated to about 30 ml., saturated with water, and again treated with carbon dioxide until precipitation was complete; the total yield of carbonate was 5·85 g. The carbonate was dissolved in excess of 2N-hydrochloric acid, and the solution evaporated to dryness, leaving a residue of 2-p-*methoxyphenylpiperidine hydrochloride* (5·57 g., 86%), m. p. 203—205°. After recrystallisation from water, the salt formed colourless prismatic needles, m. p. 204—206° (Found: C, 63·0; H, 7·9; N, 5·9. $C_{12}H_{17}ON,HCl$ requires C, 63·3; H, 8·0; N, 6·1%). Treatment of an aqueous solution of the hydrochloride with sodium hydroxide precipitated the base as an oil which soon solidified. Isolated by means of ether and purified by distillation at 155—158°/13 mm., followed by crystallisation from light petroleum (b. p. 40—60°), it formed rosettes of colourless needles, m. p. 35·5—36·5°. Crystallisation from aqueous methanol gave the hydrate, m. p. 57°, as described by van der Zanden (*Rec. Trav. chim.*, 1942, **61**, 365).

2-p-*Methoxyphenyl*-1-*methylpiperidine Methiodide*.—A mixture of the above base (1·44 g.), aqueous sodium carbonate (0·675 g. in 10 ml.), and methyl iodide (1 ml.) was warmed under reflux for 15 minutes, and the methyl iodide was then distilled off. Unchanged base was removed by ether extraction, and the aqueous phase was extracted with three 10-ml. portions of chloroform. The recovered base (0·5 g.) was remethylated for ½ hour and worked up as before. The combined chloroform extracts were dried and evaporated, leaving a brown syrup (2·34 g., 89%) which crystallised to a cream-coloured solid, m. p. 156—161°, on trituration with ether. On recrystallisation from anhydrous acetone the *methiodide* formed deliquescent, colourless, rectangular plates, m. p. 160—161° (Found: C, 48·5; H, 6·6; N, 3·7. $C_{14}H_{22}ONI$ requires C, 48·4; H, 6·4; N, 4·0%). The quaternary nature of the salt was confirmed by its failure to liberate any ether-soluble base on treatment with cold aqueous sodium hydroxide; the methiodide was recovered unchanged by extraction of the alkaline solution with chloroform. An aqueous solution of the methiodide (236 mg. in 15 ml.) was heated under reflux for 48 hours, cooled, made alkaline with aqueous sodium hydroxide and extracted with ether; evaporation of the ethereal extract left a negligible residue (0·8 mg.); the original methiodide was recovered from the aqueous solution as a light brown solid (235 mg.), m. p. 149—153°, and crystallisation from acetone gave the pure substance (149 mg.), m. p. 159—161°.

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255. *The Additive Effect of Substituents on the Strength of Benzoic Acid.*

By J. SHORTER and F. J. STUBBS.

The change in the free energy of ionisation caused by two or more substituents in benzoic acid has been shown in a number of cases to be very nearly the algebraic sum of the effects of the individual groups.

STUBBS and HINSHELWOOD (this vol., p. S 71) have shown that the velocity of benzoylation of 21 disubstituted anilines can be predicted quite accurately from those of the corresponding monosubstituted anilines. Each substituent, at a given position in the aniline, alters the free energy of activation ($-RT \ln k$) by a characteristic amount independent of the presence of another substituent. Thus the effect on the free energy of activation of two substituents in the same nucleus is very closely the sum of their individual effects.

In the present work, this principle of additivity has been examined for the free energies of *ionisation* ($-RT \ln K$) of substituted benzoic acids.

The free-energy data in the tables are calculated from classical dissociation constants taken from the International Critical Tables and the "Tabellen" of Landolt–Börnstein. Table I contains the values for benzoic acid and its mono-substituted derivatives, and the fourth column gives the *change* in the free energy of ionisation [$\Delta(-RT \ln K)$] caused by the various substituents.

TABLE I.

Acid.	$10^5 K_{25°}$.	$-RT \ln K$ (cals./mole).	$\Delta(-RT \ln K)$ (cals./mole).
Benzoic	6·69	5690	0
o-Chlorobenzoic	132	3930	−1760
m-Chlorobenzoic	15·5	5200	− 490
p-Chlorobenzoic	9·3	5500	− 190
o-Bromobenzoic	145	3870	−1820
m-Bromobenzoic	13·7	5270	− 420
p-Bromobenzoic	10·7	5420	− 270
o-Nitrobenzoic	620	3010	−2680
m-Nitrobenzoic	36	4690	−1000
p-Nitrobenzoic	38	4660	−1030
o-Hydroxybenzoic	106	4050	−1640
m-Hydroxybenzoic	8·33	5570	− 120
p-Hydroxybenzoic	2·90	6190	+ 500
o-Methoxybenzoic	8·3	5570	− 120
m-Methoxybenzoic	8·8	5540	− 150
p-Methoxybenzoic	3·2	6120	+ 430
o-Toluic	12·5	5320	− 370
m-Toluic	5·60	5800	+ 110
p-Toluic	4·30	5960	+ 270

From the results given in Table I the change in the free energy of ionisation for the polysubstituted benzoic acids can be predicted as in the following examples.

4-Nitro-3-methylbenzoic acid.

	$\Delta(-RT \ln K)$.
4-Nitro	−1030
3-Methyl	+ 110
Predicted value	− 920

2 : 3-Dinitro-5 : 6-dimethoxybenzoic acid.

	$\Delta(-RT \ln K)$.
2-Nitro	−2680
3-Nitro	−1000
5-Methoxy	− 150
6-Methoxy	− 120
Predicted value	−3950

Table II gives for 73 polysubstituted benzoic acids the observed values of $\Delta(-RT \ln K)$ and those predicted on the assumption of a strictly additive effect.

Discussion.—The results given in Tables I and II are based on investigations by a large number of different workers employing a variety of experimental methods. Many are of considerable antiquity, the concentration ranges employed vary greatly, and in certain cases the compounds may have been of questionable purity. Consequently, some of the free energies of ionisation quoted may be in error by 100 cals. or more. Therefore without performing an

unduly elaborate and tedious analysis of the data, it is not possible to do more than investigate the validity of the additivity principle to within a few units %.

An examination of Table II shows that the predicted and observed values of $\Delta(-RT \ln K)$ are frequently in close agreement. Occasionally, as with 2 : 4-dinitro- and 3-chloro-6-nitro-benzoic acids, the agreement is remarkable, while in others such as 2 : 4-dibromo- and 2-hydroxy-4-methyl-benzoic acids there is agreement to within 5%. When the total effect of the substituents is comparatively small, considerable discrepancies reckoned as percentages are only to be expected, although in examples such as 3 : 5-dimethyl- and 3-hydroxy-2-methyl-benzoic acids, the discrepancy in calories is quite small.

There are, however, certain cases in which the total effect of the substituents is considerable, and the additivity principle is seriously violated. These are worthy of more detailed consideration.

Compounds containing two groups ortho to the carboxyl group often show serious discrepancies; *e.g.*, 2 : 6-dimethyl-, 2 : 6-dinitro-, and 2 : 6-dihydroxy-benzoic acids. Others, however, *e.g.*, 2 : 4 : 6-tribromobenzoic acid, do not. Some, at any rate, of these discrepancies are probably real and not due to gross experimental error. Rather convincing evidence for this view exists in a few of the examples. If the effect be real, an improved prediction for a trisubstituted benzoic acid containing two *ortho*-groups should be possible from the experimental value for the 2 : 6-disubstituted-benzoic acid, *e.g.*, a new value of $\Delta(-RT \ln K)$ for 2 : 4 : 6-trihydroxybenzoic acid may be derived from the results for 2 : 6-dihydroxy- and *p*-hydroxy-benzoic acids. Some illustrations of this procedure are given in Table III.

TABLE II.

Substituted benzoic acid.	$10^5 K_{25}$.	$\Delta(-RT \ln K)$, cals./mole : Observed.	Predicted.
2 : 4-Dibromo-	200	−2010	−2090
2 : 3-Dinitro-	1300	−3110	−3680
2 : 4-Dinitro-	3500	−3700	−3710
2 : 5-Dinitro-	2400	−3480	−3680
2 : 6-Dinitro-	7450	−4150	−5360
3 : 4-Dinitro-	150	−1840	−2030
3 : 5-Dinitro-	160	−1870	−2000
2 : 3-Dihydroxy-	114	−1680	−1760
2 : 4-Dihydroxy-	50·5	−1190	−1140
2 : 5-Dihydroxy-	108	−1640	−1760
2 : 6-Dihydroxy-	500	−3920	−3280
3 : 4-Dihydroxy-	3·3	+ 420	+ 380
3 : 5-Dihydroxy-	9·1	− 180	− 240
3 : 4-Dimethoxy-	3·54	+ 380	+ 280
2 : 4-Dimethyl-	9·0	− 170	− 100
2 : 5-Dimethyl-	12	− 340	− 260
2 : 6-Dimethyl-	62	−1310	− 740
3 : 5-Dimethyl-	4·8	+ 200	+ 220
2-Chloro-3-nitro-	870	−2880	−2760
2-Chloro-4-nitro-	1000	−2960	−2790
2-Chloro-5-nitro-	620	−2580	−2760
3-Chloro-2-nitro-	440	−2470	−3170
3-Chloro-5-nitro-	74·1	−1420	−1490
3-Chloro-6-nitro-	1400	−3170	−3170
4-Chloro-2-nitro-	1000	−2960	−2870
4-Chloro-3-nitro-	46	−1130	−1190
2-Chloro-3-hydroxy-	136	−1780	−1880
2-Chloro-5-hydroxy-	138	−1790	−1880
3-Chloro-4-hydroxy-	5·6	+ 110	+ 10
5-Chloro-2-hydroxy-	195	−1990	−2130
2-Chloro-5-methoxy	130	−1750	−1910
2-Bromo-3-nitro-	1200	−1710	−2820
2-Bromo-5-nitro-	910	−2910	−2820
3-Bromo-2-nitro-	300	−2250	−3100
3-Bromo-6-nitro-	1400	−3170	−3100
4-Bromo-3-nitro-	42	−1080	−1270
5-Bromo-2-hydroxy-	240	−2120	−2060
3-Nitro-2-hydroxy-	1500	−3210	−2640

TABLE II (*continued*).

Substituted benzoic acid.	10^5K_{25}.	$\Delta(-RT \ln K)$, cals./mole Observed.	Predicted.
5-Nitro-2-hydroxy-	780	−2810	−2640
3-Nitro-4-methoxy-	19	− 620	− 570
4-Nitro-3-methyl-	31	− 900	− 920
4-Hydroxy-3-methoxy-	2·94	+ 490	+ 350
2-Hydroxy-3-methyl-	100	−1600	−1530
2-Hydroxy-4-methyl-	72	−1410	−1370
2-Hydroxy-5-methyl-	86	−1500	−1530
2-Hydroxy-6-methyl-	104	−1630	−2010
3-Hydroxy-2-methyl-	16·6	− 530	− 490
2-Methoxy-4-methyl-	4·04	+ 300	+ 150
2-Methoxy-5-methyl-	6·65	+ 10	− 10
4-Methoxy-2-methyl-	5·2	− 150	− 60
4-Methoxy-3-methyl-	3·4	− 410	− 540
2 : 4 : 6-Tribromo-	390	−3770	−3910
2 : 4 : 6-Trihydroxy-	2100	−3400	−2780
2 : 3 : 4-Trimethyl-	3·3	+ 410	+ 10
2 : 4 : 5-Trimethyl-	9·5	− 210	+ 10
2 : 4 : 6-Trimethyl-	37	−1010	− 470
2 : 6-Dichloro-3-hydroxy-	2100	−3400	−3640
3 : 5-Dichloro-2-hydroxy-	450	−2490	−2620
2-Chloro-6-bromo-3-hydroxy-	2200	−3430	−3700
2-Chloro-6-bromo-5-hydroxy-	200	−2010	−3700
2-Nitro-3 : 4-Dimethoxy-	79	−1460	−2400
2-Nitro-4 : 5-dimethoxy-	320	−2290	−2400
3-Nitro-2 : 5-dimethoxy-	170	−1910	−1270
4-Nitro-2-hydroxy-5-methoxy-	1000	−2960	−2820
5-Nitro-2-hydroxy-3-methoxy	900	−2890	−2790
5-Nitro-3-hydroxy-4-methoxy-	270	− 820	− 690
5-Nitro-4-hydroxy-3-methoxy-	170	− 550	− 650
2 : 6-Dihydroxy-4-methyl-	4100	−3790	−3010
2 : 3 : 4 : 5-Tetramethyl-	6·0	+ 70	+ 120
2 : 3 : 4 : 6-Tetramethyl-	10	− 230	− 360
2 : 3 : 5 : 6-Tetramethyl-	30	− 890	− 520
2 : 3-Dinitro-5 : 6-dimethoxy-	4400	−3830	−3950
2 : 3-Dinitro-4-hydroxy-5 : 6-dimethyl-	4600	−3860	−3440

TABLE III.

Substituted benzoic acid.	$\Delta(-RT \ln K)$, cals./mole: Observed.	New predicted.	Old predicted.
2 : 4 : 6-Trihydroxy-	−3400	−3420	−2780
2 : 4 : 6-Trimethyl-	−1010	−1040	− 470
2 : 6-Dihydroxy-4-methyl-	−3790	−3650	−3010
2 : 3 : 5 : 6-Tetramethyl-	− 890	−1100 *	− 520

* From 2 : 6- and 3 : 5-dimethylbenzoic acids.

The great improvement in the predictions seems to show that for 2 : 6-dimethyl- and 2 : 6-dihydroxy-compounds at least, the effect is real and takes the form of an enhancement of the influence of the groups. This " di-*ortho* " effect for 2 : 6-dinitro- and 2-hydroxy-6-methyl compounds would be of the nature of a " saturation effect ".

It is interesting to note that Stubbs and Hinshelwood (*loc. cit.*) found no violation of the additivity principle for free energy of activation in the benzoylation of 2 : 6-dimethylaniline.

If one of a given pair of substituents be placed in the *ortho*-position and the other in either of the two *meta*-positions, the two compounds should, according to the additivity principle, have the same value of $\Delta(-RT \ln K)$. For certain pairs, *e.g.*, 2 : 3- and 2 : 5-dihydroxybenzoic acids, and 2-hydroxy-3-methyl- and 2-hydroxy-5-methyl-benzoic acids, this holds. In others, however, *e.g.*, 2 : 3- and 2 : 5-dinitro-, and also 3-chloro-2-nitro- and 3-chloro-6-nitro-benzoic acids, the " 2 : 3 " compound shows a serious discrepancy.

It may be concluded, therefore, that while the additivity principle holds for free energies of

ionisation of a number of polysubstituted benzoic acids, marked discrepancies occur with certain 2 : 6- and 2 : 3-compounds.

[*Added in proof.*] Since this paper was written, it has come to our notice that Wegsheider (*Monatsh.*, 1902, **23**, 288) examined the effect of substituents on strength for a number of aromatic acids (mainly monoesters of phthalic acids) in terms of "factors," a procedure which is analogous to that employed above. He found the effect of groups to be very approximately additive, except for certain 2 : 6- and 2 : 3-compounds.

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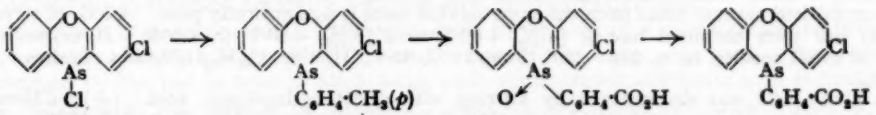
256. *The Configuration of Heterocyclic Compounds. Part XII. The Optical Resolution of* 2-*Chloro*-10-p-*carboxyphenylphenoxarsine.*

By MARY S. LESSLIE.

2-Chloro-10-*p*-carboxyphenylphenoxarsine has been resolved by means of the strychnine and cinchonine salts. The active acids, $[\alpha]_{5791}^{20°}$ +162·1° and −161·3° in chloroform, showed high optical stability.

IN Part XI of this series (Campbell, *J.*, 1947, 4) the resolution of 10-*p*-carboxyphenyl-2-methylphenoxstibine was described. The active acids were found to undergo racemisation in boiling alcohol whereas the optically active phenoxarsines (Lesslie and Turner, *J.*, 1934, 1170; 1935, 1268; 1936, 730; Lesslie *J.*, 1938, 1001) had shown high optical stability. It was suggested by Campbell that one of the factors contributing to the optical instability of the phenoxstibine might be the heavy polar *p*-carboxyphenyl group in the 10-position which might encourage inversion of the pyramidal configuration of the antimony atom. It therefore seemed desirable to prepare a similar 10-*p*-carboxyphenylphenoxarsine to see if the optical stability of the phenoxarsine was affected. 2-*Chloro*-10-p-*carboxyphenylphenoxarsine* was synthesised, and a number of its alkaloidal salts were examined. The (±)-acid was prepared according to the following scheme:



The strychnine salt crystallised from a 1 : 1 mixture of chloroform and alcohol, and after repeated recrystallisation from the same solvent the optically pure strychnine (+)-acid *salt*, $[\alpha]_{5791}^{20°}$ +69·7° and $[\alpha]_{5461}^{20°}$ +80·7° in chloroform, was obtained. The *acid* regained from this salt had $[\alpha]_{5791}^{20°}$ +162·1° and $[\alpha]_{5461}^{20°}$ +187·5°. The more soluble strychnine salt was recrystallised from alcohol until the rotation was constant, $[\alpha]_{5791}^{20°}$ −100·6° and $[\alpha]_{5461}^{20°}$ −115·3°, but the acid obtained from it, $[\alpha]_{5791}^{20°}$ −128·3° and $[\alpha]_{5461}^{20°}$ −148·3° in chloroform, was not optically pure.

The quinine salts were examined, but again complete separation of the diastereoisomers could not be effected. The more sparingly soluble (−)-acid salt was recrystallised 8 times from alcohol; the rotation was then constant $[\alpha]_{5791}^{20°}$ −177·2° and $[\alpha]_{5461}^{20°}$ −203·4° in chloroform. The acid obtained from this salt, however, had $[\alpha]_{5791}^{20°}$ −138·0° and $[\alpha]_{5461}^{20°}$ −159·6°. No attempt was made to purify the more soluble (+)-acid salt.

The optically impure (−)-acid was converted into the cinchonine salt, and after 13 recrystallisations from alcohol the optically pure cinchonine (−)-acid *salt* had $[\alpha]_{5791}^{20°}$ −12·3° and $[\alpha]_{5461}^{20°}$ −15·9° in chloroform. The acid regenerated from this salt had $[\alpha]_{5791}^{20°}$ −161·3° and $[\alpha]_{5461}^{20°}$ −187·1°.

During the above resolution experiments there was no indication that prolonged boiling in alcoholic solution of any of the alkaloidal salts led to asymmetric transformation (cf. Campbell, *J.*, 1947, 4). The active acids were also unaffected when their solutions in either chloroform or alcohol were boiled for 1 hour. After a solution of the (+)-acid in 0·5N-sodium hydroxide had been boiled for 3 hours the rotation of the recovered acid was unchanged. The optical stability of the phenoxarsines would therefore appear to be unaffected by the *p*-carboxyphenyl group in the 10-position.

Experimental.

Carbon and hydrogen analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected. Rotations were observed in chloroform in 2 dm. tubes.

2 : 10-*Dichlorophenoxarsine.*—This substance was synthesised by the method of Roberts and Turner (*J.*, 1925, 2004) by reduction of 2-chlorophenoxarsonic acid. The acid (50 g.) was suspended in a mixture of concentrated hydrochloric acid and chloroform containing a little iodine, and reduced at 50° by passing in sulphur dioxide. The product was a mixture of 2 : 10-dichlorophenoxarsine, m. p. 144—145°, and 2-*p*-chlorophenoxyphenyldichloroarsine, m. p. 67—68° (*J.*, 1925, 2004), in the ratio 2 : 1. Separation was effected by crystallisation from chloroform in which solvent the dichlorophenoxarsine was the more sparingly soluble. Reduction of the chloroform mother-liquor gave crude 2-*p*-chlorophenoxyphenyldichloroarsine which was purified by crystallisation from light petroleum (b. p. 60—80°). It was converted into the required 2 : 10-dichlorophenoxarsine by distillation under reduced pressure. The above reduction was repeated several times, and always resulted in a mixture of the two chloroarsines being obtained. Roberts and Turner reported an arsenic-free substance isolated from their reduction product, but in the above reductions no trace of it was evident.

2-*Chloro*-10-p-*tolylphenoxarsine.*—To the decanted Grignard reagent prepared from *p*-bromotoluene (208 g.; 4 mols.) was added a solution in benzene (300 c.c.) of 2 : 10-dichlorophenoxarsine (95 g.; 1 mol.). The solution was heated in boiling water for 9 hours, the ether being allowed to distil gradually. The product was decomposed with ice and dilute hydrochloric acid. The benzene solution was separated, washed, and dried, and the solvent removed. The residue was distilled in a vacuum, and 88 g. (80% yield) of the *arsine* were obtained as a viscous oil, b.p. 260—264°/10 mm. It crystallised on being stirred with a mixture of acetone and light petroleum. It was recrystallised from alcohol; needles, m. p. 70—71° (Found: C, 61·5; H, 4·1; As, 20·6. $C_{19}H_{14}OClAs$ requires C, 61·9; H, 3·8; As, 20·3%).

2-*Chloro*-10-p-*carboxyphenylphenoxarsine* 10-*Oxide.*—The foregoing arsine (30 g.) was suspended in a solution of potassium permanganate (30 g.) in water (800 c.c.), and the mixture boiled under reflux for 3 hours. Sulphur dioxide was then passed into the solution, and the *oxide-acid* was precipitated. It was collected and purified through the sparingly soluble sodium salt. Crystallised from glacial acetic acid it formed rectangular prisms, m. p. 325—326° (Found: C, 54·7; H, 2·9; As, 18·1. $C_{19}H_{12}O_4ClAs$ requires C, 55·0; H, 2·9; As, 18·1%).

2-*Chloro*-10-p-*carboxyphenylphenoxarsine.*—The preceding oxide-acid (33 g.) was suspended in dilute hydrochloric acid and chloroform containing a little iodine; sulphur dioxide was passed into the warmed mixture for about 1½ hours, the chloroform being allowed to evaporate gradually but completely. The *acid* was collected and crystallised from alcohol, needles (25 g.), m. p. 226—227°, being obtained (Found: C, 57·2; H, 3·2; As, 18·8. $C_{19}H_{12}O_3ClAs$ requires C, 57·2; H, 3·0; As, 18·8%).

Resolution with Strychnine.—To the (±)-acid (12 g.) dissolved in boiling alcohol (500 c.c.) was added a solution of strychnine (10 g.) in warm chloroform (100 c.c.). The first fraction *A* (7 g.) which separated overnight had $[\alpha]_{5791}^{20°}$ +49·3° (*c*, 0·902). The mother-liquor was reduced to 450 c.c., and a second crop *B* (7·9 g.) separated which had $[\alpha]_{5791}^{20°}$ −16·9° (*c*, 1·124). On further reduction of the mother-liquor to 200 c.c. a third crop *C* (5·5 g.) was obtained which had $[\alpha]_{5791}^{20°}$ −99·5° (*c*, 1·126). Salt *A* was recrystallised 4 times from alcohol–chloroform and thereafter remained constant in rotation. Salt *B* was recrystallised several times from the same solvent until it was optically pure. 4·5 G. of strychnine (+)-acid *salt* were obtained having $[\alpha]_{5791}^{20°}$ +69·7° and $[\alpha]_{5461}^{20°}$ +80·7° (*c*, 1·055). It crystallised in clumps of small needles, m. p. 249—250° (Found: C, 64·9; H, 4·8. $C_{40}H_{34}O_5N_2ClAs$ requires C, 65·5; H, 4·7%).

The above salt was decomposed by stirring with dilute hydrochloric acid. (+)-2-*Chloro*-10-p-*carboxyphenylphenoxarsine* crystallised from alcohol in very slender needles, m. p. 219—220°. It had $[\alpha]_{5791}^{20°}$ +162·1° and $[\alpha]_{5461}^{20°}$ +187·5° (*c*, 0·944) (Found: C, 57·2; H, 2·9. $C_{19}H_{12}O_3AsCl$ requires C, 57·2; H, 3·0%). Salt *C* after a number of recrystallisations from alcohol had constant rotation, $[\alpha]_{5791}^{20°}$ −100·6° and $[\alpha]_{5461}^{20°}$ −115·3° (*c*, 0·984); nevertheless, the acid recovered from this salt had $[\alpha]_{5791}^{20°}$ −128·3° and $[\alpha]_{5461}^{20°}$ − 148·3° (*c*, 0·998), and it was obvious that the (−)-acid salt and the partial racemate could not be separated. All the fractions of optically impure salt were decomposed with dilute hydrochloric acid, and after crystallisation from alcohol the recovered acid had $[\alpha]_{5791}^{20°}$ −37·4° and $[\alpha]_{5461}^{20°}$ −42·5° (*c*, 1·471).

Attempted Resolution with Quinine.—The acid ($[\alpha]_{5791}^{20°}$ −37·4°) (7·3 g.) and quinine (5·9 g.) were dissolved in boiling alcohol (400 c.c.); during the night 7·6 g. of salt separated in rosettes of sheaves of fine needles, having $[\alpha]_{5791}^{20°}$ −129·5° and $[\alpha]_{5461}^{20°}$ −149·7° (*c*, 0·994). After 6 recrystallisations from alcohol the rotation remained constant, $[\alpha]_{5791}^{20°}$ −177·2° and $[\alpha]_{5461}^{20°}$ −203·4° (*c*, 1·064). The salt was decomposed with dilute hydrochloric acid, and after crystallisation from alcohol the acid had $[\alpha]_{5791}^{20°}$ −133·9° and $[\alpha]_{5461}^{20°}$ −156·3° (*c*, 1·075). Recrystallisation of the acid did not affect the rotation.

Resolution with Cinchonine.—The acid ($[\alpha]_{5791}^{20°}$ −133·9°) (4·95 g.) and cinchonine (3·6 g.) were dissolved in boiling alcohol (130 c.c.). The solution after standing overnight deposited 6·9 g. of salt having $[\alpha]_{5791}^{20°}$ +17·9° and $[\alpha]_{5461}^{20°}$ +19·3° (*d*, 1·087). It was recrystallised 13 times from alcohol, and the rotation by then remained constant. The cinchonine (−)-acid *salt* crystallised in small rods, m.p. 139—140°, $[\alpha]_{5791}^{20°}$ −12·3° and $[\alpha]_{5461}^{20°}$ −15·9° (*c*, 0·972) (Found: C, 65·5; H, 5·0. $C_{38}H_{34}O_4N_2ClAs$ requires C, 65·8; H, 4·9%). (−)-2-*Chloro*-10-p-*carboxyphenylphenoxarsine* crystallised from alcohol in slender needles, m. p. 219—220°. It had $[\alpha]_{5791}^{20°}$ −161·3° and $[\alpha]_{5461}^{20°}$ −187·1° (*c*, 0·930) (Found: C, 57·5; H, 3·1. $C_{19}H_{12}O_3ClAs$ requires C, 57·2; H, 3·0%).

The active acids were sensitive to light, and on exposureto sunlight became pink. This sensitivity was not observed in the racemic acid.

0·2 G. of pure (+)-acid were boiled under reflux with 0·5N-sodium hydroxide for 3 hours. The crude acid recovered had $[\alpha]_{5791}^{20°}$ +161·6° and $[\alpha]_{5461}^{20°}$ +187·2° (*c*, 0·956).

Bedford College, University of London. [*Received, November 12th*, 1948.]

257. *Substitution in the γ-Pyrone Nucleus: Derivatives of Pyromeconic Acid.*

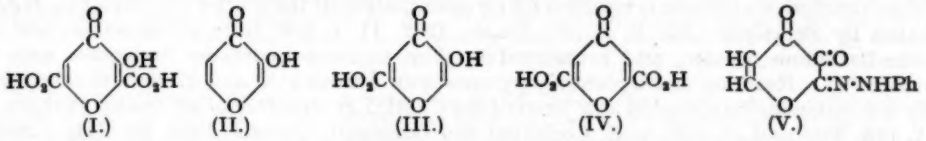
By Edwin L. Shimmin and Frederick Challenger.

The bromo- and amino-derivatives of pyromeconic acid have been examined with regard to their possible use as synthetic reagents.

An improved method of bromination is described and evidence suggested for the orientation of the nitro- and amino-derivatives of pyromeconic acid.

The acetyl, benzoyl, and benzenesulphonyl derivatives of aminopyromeconic acid have also been prepared.

Dry distillation of anhydrous meconic acid (I) with copper-bronze causes the loss of two carboxyl groups from one molecule of the acid (Robiquet, *Annalen*, 1833, **5**, 102; Ihlée, *ibid.*, 1877, **188**, 31; Borsche, *Ber.*, 1916, **49**, 2544; Peratoner and Leone, *Gazzetta*, 1894, **24**, ii, 78) producing at best a 45% yield of pyromeconic acid (II). We find that, under reduced pressure, a mixture of 43% pyromeconic acid and 57% comenic acid (III) results, which is analogous to the increase in yield of comanic acid when chelidonic acid (IV) is also distilled in vacuum (Haitinger and Lieben, *Monatsh.*, 1885, **6**, 279). Bromopyromeconic acid was prepared by the

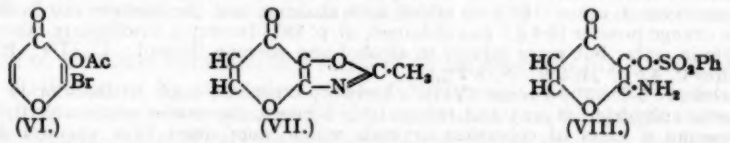


methods of Brown (*Annalen*, 1852, **84**, 41) and Compagno (*Atti R. Accad. Lincei*, 1908, **17**, i, 78), and by numerous variations of the known methods of bromination, but the extremely low yields indicated that oxidation rather than bromination was favoured by acid solutions. By the use of buffer solutions the pH was adjusted to give yields as high as 85%, a result of importance in view of the high cost of meconic acid. This method has also been successfully applied to the preparation of bromokojic acid (Barnard, Thesis, Leeds, 1947).

The bromine atom in bromopyromeconic acid is completely inert, owing to the pronounced effect of the unsaturated ring, disintegration taking place in all cases before any reaction occurred. The hydroxyl group behaves normally, yielding an *acetyl* derivative (VI).

The nitration of pyromeconic acid was studied, nitric acid of various concentrations and nitrous fumes in various media and at different temperatures being employed. The yield was not improved by the use of fuming nitric acid, and concentrated sulphuric acid increased the rate of oxidation at the expense of nitration. Also, oxidation and not nitration occurred at temperatures below 34°, while partial nitration took place during the course of the violent reaction above this temperature. Urea (0·1 g. to 1 g. of pyromeconic acid) moderated the violence of the reaction to some extent but gave no increase in yield, whilst if 0·2 g. or more of urea was present the vigorous reaction did not take place below 36° or higher, and oxidation was favoured. The method finally adopted was a modification of that of Ost (*J. pr. Chem.*, 1879, **19**, 189), who had already prepared the explosive sodium and silver salts (*loc. cit.*). The *ferric* salt was also found to be explosive. The silver atom in silver nitropyromeconate resisted all attempts at substitution. The O-*methyl* derivative was prepared by means of diazomethane.

Electrolytic and catalytic methods of reduction of nitropyromeconic acid to the amino-compound being found unsuitable, this compound was isolated as the hydrochloride by Ost's method (*loc. cit.*), which, though laborious, gave a 75% yield. The usual methods of diazotisation were tried without success, resulting only in oxidation and disintegration of the molecule. There was no evidence of the formation of an internal diazo-oxide which might have been expected owing to the presence of the *o*-hydroxyl group.



Aminopyromeconic acid reacts readily with acetic anhydride and, as would be expected, both the hydroxyl and the amino-group are involved. The product appears to be 2-*methyl*-

oxazolo(4 : 5-2′ : 3′)*pyrone* (VII). Benzoylation of both groups proceeded normally in very weak alkaline solution, though in pyridine a tar was produced. Mild hydrolysis with dilute alkali removed the acyl group attached to the hydroxyl, but prolonged alkaline hydrolysis was required to remove the *N*-benzoyl group, in the course of which there was some fission of the ring.

The O-*benzenesulphonyl* derivative (VIII) has the acyl group attached to hydroxyl. The acylation was carried out in a saturated solution of sodium hydrogen carbonate, it being found that the sensitive γ-pyrone ring was rendered even more so in this compound; the use of pyridine as a medium caused vigorous decomposition and formation of a tar. Very dilute sodium hydroxide, of a concentration usually without action on these compounds, produced immediate disintegration giving hydroxyacetone.

Since many derivatives of pyromeconic acid contain the substituent in the 2-position (Files and Challenger, *J.*, 1940, 665), it seemed probable that the nitro- and the amino-group also occupy this 2-position. The composition of the acetyl derivative is in agreement with the formula (VII) which requires the NH_2 in the 2-position. Nitropyromeconic acid was decomposed on heating with acetyl chloride for 1 hour or on warming with acetic anhydride. The yellow colour, like that of 2-nitro-3-hydroxyfuran (Hodgson and Davies, *J.*, 1939, 1013), suggests chelation. The methyl ether was readily prepared by using diazomethane.

More conclusive evidence is afforded by an examination of the scarlet compound $C_{11}H_8O_3N_2$ prepared by Peratoner (*Atti R. Accad. Lincei*, 1902, **11**, i, 250) from pyromeconic acid and benzenediazonium acetate, and considered by him to be a hydrazine derivative with the structure (V). Reaction of 3-hydroxy-γ-pyrones with nitrous acid and diazonium salts occurs in the 2-position and is accepted as a proof of the C(OH):CH structure of allomaltol (Yabuta, *J.*, 1924, **125**, 576) and of kojic acid (Corbellini and Gregorini, *Gazzetta*, 1930, **60**, 244). Maltol, containing the group C(OH):C(CH_3), does not react with these reagents (Peratoner and Tamburello, *ibid.*, 1906, **36**, i, 41).

The scarlet compound, on reduction with tin and hydrochloric acid, gave aminopyromeconic acid, identified by its colour reaction with ferric chloride and by the m. p. (182°) of its dibenzoyl derivative. It is therefore concluded that both the amino- and the nitro-group occupy the 2-position.

Experimental.

2-*Bromopyromeconic Acid.*—(A) Bromine (3·5 g.) was dissolved in saturated sodium acetate solution (100 c.c.) and 75 c.c. of this solution added at 0° to a solution of pyromeconic acid (2 g.) in glacial acetic acid (5 c.c.). After 1 hour the bromopyromeconic acid (1·8 g.) was filtered off and recrystallised from alcohol.

(B) A solution of pyromeconic acid (2 g.) in orthophosphoric acid (12 c.c.) was treated at 0° with the above bromine solution (85 c.c.). The yield after recrystallising from alcohol was 2·87 g. Attempts to remove the bromine atom or to cause ring-linkage by reaction with silver, silver oxide, silver cyanide, copper-bronze, sodium thiocyanate, sodium and methyl iodide, and aniline failed, although various solvents, temperatures and conditions, including heating in sealed tubes, were tried.

2-*Bromo*-O-*acetylpyromeconic Acid.*—2-Bromopyromeconic acid (0·5 g.) and acetyl chloride (5 c.c.) were refluxed for 5 hours, and most of the excess acetyl chloride distilled off. The colourless solid obtained on cooling, when recrystallised from benzene–light petroleum, had m. p. 99°, and was very soluble in chloroform, benzene, and water but sparingly soluble in ether; long boiling with water was required before hydrolysis was effected, and a coloration obtained with ferric chloride (Found: Br, 33·7; Ac, 18·4. $C_7H_5O_4Br$ requires Br, 34·4; Ac, 18·45%).

2-*Nitropyromeconic Acid.*—Ost's method (*loc. cit.*) was modified to obtain consistent yields; pyromeconic acid (2 g.) was dissolved in glacial acetic acid (6 c.c.) in a large tube (roughly 9″ × 1″) and immersed in ice–salt, nitric acid (*d* 1·41; 1·5 c.c.) being added with shaking until the nitrate had been precipitated. The tube was then cautiously warmed over a small flame to start a strictly localised reaction, the tube being again plunged into the freezing mixture as soon as brown fumes were observed. The reaction, though very violent, was not explosive and gave a yield of 0·8 g. The *ferric* salt was obtained by adding a concentrated aqueous solution of ferric chloride to a cold saturated solution of the sodium salt. Great care must be exercised, since the precipitate is very soluble in slight excess of ferric chloride. The dry red salt is explosive on warming, soluble in alcohol, but sparingly in water.

Nitropyromeconic Acid Methyl Ether.—Nitropyromeconic acid (8 g.) was suspended in dry ether. excess of diazomethane in ether (160 c.c.) added with shaking, and the mixture left in the refrigerator overnight. An orange powder (8·4 g.) was obtained, m. p. 88° (decomp.), insoluble in ether and benzene, sparingly soluble in water but more soluble in alcohol and acetone (Found: C, 41·9; H, 3·4; N, 8·7, $C_6H_5O_5N$ requires C, 42·1; H, 2·9; N, 8·2%).

2-*Methyloxazolo*(4 : 5-2′ : 3′)*γ-pyrone* (VII).—Aminopyromeconic acid hydrochloride (0·7 g.) was dissolved in acetic anhydride (8 c.c.) and refluxed for 3 hours, the excess acetic anhydride being then distilled off, leaving a mass of colourless crystals which were dried in a vacuum desiccator and recrystallised from chloroform; m. p. 137° (Found: C, 55·82; H, 3·3; N, 9·25; Ac, 27·8. $C_7H_5O_3N$ requires C, 55·65; H, 3·3; N, 9·3; Ac, 28·5%). They were insoluble in benzene, ether, and light petroleum, but easily soluble in acetone, chloroform, alcohol, and water. The cold aqueous solution gave no

coloration with ferric chloride even after long standing, and at least 30 minutes' boiling with water was required before hydrolysis was noticeable. Refluxing for 3 hours in presence of hydrochloric acid produced crystals of the original amine hydrochloride.

ON-*Dibenzoylaminopyromeconic Acid.*—The hydrochloride (0·5 g.) was dissolved in ice-water (20 c.c.), and benzoyl chloride added with vigorous shaking. An ice-cold N-solution of sodium hydroxide was added dropwise to maintain faint alkalinity. The white precipitate obtained after 20 minutes was redissolved in a few drops of alkali, and the mixture filtered and acidified with dilute hydrochloric acid, a white solid being obtained. This was separated, shaken several times with ether, and recrystallised from alcohol. The colourless crystals, m. p. 182°, were very soluble in acetone, sparingly in hot water, and insoluble in ether and benzene; yield, 0·54 g. (Found: C, 68·6; H, 3·9; N, 4·1. $C_{18}H_{13}O_5N$ requires C, 68·1; H, 3·9; N, 4·1%).

Benzamidopyromeconic Acid.—The dibenzoyl derivative was dissolved in very dilute sodium hydroxide, heated for 10 minutes on the steam-bath, giving a bright yellow solution, and then acidified with dilute hydrochloric acid, giving a white crystalline solid on cooling. This was recrystallised from alcohol in which it was sparingly soluble; m. p. 232° (decomp.). The aqueous solution gave a strong violet coloration with ferric chloride, indicating the presence of phenolic hydroxyl (Found: C, 61·95; H, 4·1; N, 5·5. $C_{11}H_9O_4N$ requires C, 62·3; H, 3·9; N, 6·06%). Treatment with benzoyl chloride and alkali reconverted this compound into the dibenzoyl derivative.

O-*Benzenesulphonylaminopyromeconic Acid* (VIII).—Aminopyromeconic acid hydrochloride (0·5 g.) in ice-water (5 c.c.) and cold saturated sodium hydrogen carbonate solution (10 c.c.) was treated with benzenesulphonyl chloride (1·5 c.c.), the mixture being kept in ice–salt. The white precipitate, when recrystallised from hot dilute hydrochloric acid and again from water, had m. p. 169° (yield 0·64 g.). With pyridine as solvent there was no reaction in the cold, but at room temperature vigorous decomposition occurred with production of tar. Prolonged acid hydrolysis liberated the parent amine from the compound, which, since it gave no coloration with ferric chloride, was clearly an O-*benzenesulphonyl* derivative (Found: C, 49·8; H, 3·4; S, 12·0; N, 5·6. $C_{11}H_9O_5NS$ requires C, 49·45; H, 3·4; S, 12·0; N, 5·25%).

The benzenesulphonyl derivative in water was boiled under reflux, and sodium hydroxide added dropwise during 10 minutes. The mixture was then acidified and concentrated. It gave a yellow dinitrophenylhydrazone, which was washed with aqueous sodium carbonate to remove any pyruvic acid 2 : 4-dinitrophenylhydrazone. It then had m. p. 299° and gave a deep blue-violet colour with alcoholic sodium hydroxide. These reactions indicate the presence of hydroxyacetone. Under the same conditions aminopyromeconic acid was stable during 30 minutes.

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258. *Reactions of Aromatic Nitro-compounds with Alkaline Sulphides. Part III. Dinitronaphthalenes.*

By HERBERT H. HODGSON and EDWARD R. WARD.

A dinitronaphthalene reacts with alkali sulphides, and in particular with sodium hydrogen sulphide to form, mainly, a monoamine by reduction, and a sodium mercaptide by replacement of a nitro- with a sodium-thio- (SNa-)group, the ratio of these products varying according to the electropositivity of the carbon atom to which the reactive nitro-group is attached. 1 : 2- or 1 : 8-Dinitronaphthalene gives only mercaptan, whereas the 1 : 3-, 1 : 5-, 1 : 6-, and 2 : 7-isomers give mainly the amine. 1 : 4-Dinitronaphthalene behaves like the 1 : 2-isomer, except that *ca.* 4% of monoamine is also formed. The results are in accord with Hodgson's theory of sulphide reduction and with the previous conclusions of the present authors.

IN former reductions of dinitronaphthalenes with alkaline sulphides, the low yield of amine which generally occurred was thought to be due to the formation of sulphur dyes or of similar complexes (cf. Hodgson and Ward, *J.*, 1945, 663, 794), but it has now been established that these by-products are produced only in traces, if at all, when pure reagents are used and, in particular, the pure sodium hydrogen sulphide of Hodgson and Ward (*J.*, 1948, 242). Reactions of various alkaline sulphides with numerous dinitronaphthalenes are now reported, together with supplementary information from similar experiments with α- and β-nitronaphthalene, α- and β-naphthylhydroxylamine, αα′-azoxynaphthalene, and 1 : 3 : 8-trinitro- and 1 : 3 : 6 : 8-tetranitro-naphthalene.

In addition to the direct reduction of a nitro- to an amino-group, there occurs a considerable replacement of the nitro- by the sodium-thio- (SNa-)group, the extent of this replacement varying according to the electropositivity of the carbon atom to which the nitro-group is attached; for example, there is only replacement of the nitro-group in 1 : 2-dinitronaphthalene, in which C_1 has the higher positivity, very largely owing to the combined electron-attracting effects of the 2-nitro-group and the negative inductive ($-I$) effect (Hodgson and Elliott, *J.*,

1935, 1850; *J. Soc. Dyers and Col.*, 1938, **54**, 264) of the second nucleus. In many cases, owing to the labile character of the sodium mercaptide formed, it has proved very difficult to isolate this or the disulphide obtained from it by oxidation. The replacement occurs in both the poly- and mono-nitronaphthalene series.

In most of the work now described, sodium hydrogen sulphide (Hodgson and Ward, *loc. cit.*) was caused to react in just definite excess with the dinitro- or other nitro-naphthalene in solution or suspension in aqueous methanol. The insoluble part of the product usually contained an amine, organic sulphide, and unchanged reactant; the solution contained a mercaptide which, in most cases, immediately began to oxidise to disulphide, a process doubtless aided by the sodium nitrite liberated by the replacement reaction. The stability of the mercaptide depends on the position of the remaining nitro-group in the nucleus. *E.g.*, that from 1 : 2-dinitronaphthalene is stable for a comparatively long time, and that from the 1 : 5-isomer was more stable than that from 1 : 6-dinitronaphthalene; these results are in accord with the quinonoid hypothesis of Veselý and Jakes (*Bull. Soc. chim.*, 1923, **33**, 955), amplified by Hodgson and Hathway (*J. Soc. Dyers and Col.*, 1945, **61**, 283; 1946, **62**, 241) and by Hodgson and Ward (*ibid.*, 1947, **63**, 141, 177), for this predicts that the 2- and 5-nitro-groups should cause greater electronic attraction at C_1 (*i.e.*, pronounced positive character of the carbon atom to which the sodium-thio-group is attached) than does the 6-nitro-group in a non-quinonoid position.

The sulphur compounds associated with the amine are usually a disulphide, formed by oxidation during manipulation, and a monosulphide formed by interaction of the reactive nitro-group of the initial material with the mercaptan produced by replacement.

Strong evidence for mercaptide formation, *e.g.*, with 1 : 8- and 2 : 7-dinitronaphthalene, is provided, when isolation is difficult, by computation of the amounts of sodium hydrogen sulphide used for reduction and replacement, respectively, in comparison with the actual amount consumed. Direct proof has also been obtained in several cases by oxidation to the disulphide and isolation of the thiolacetate (SAc) derivative. The following table summarises the results of the reactions of sodium hydrogen sulphide with seven dinitronaphthalenes.

Dinitronaphthalene.	Products formed.
1 : 2-	2 : 2′-Dinitro-1 : 1′-dinaphthyl sulphide, and 2-nitro-1-naphthalenethiol. Sodium disulphide also gave the monosulphide (with sulphur).
1 : 3-	A mixture (82%) of 3-nitro-1-naphthylamine and 4-nitro-2-naphthylamine (cf. Hodgson and Birtwell, *J.*, 1944, 75).
1 : 4-	4 : 4′-Dinitro-1 : 1′-dinaphthyl sulphide, 4-nitro-1-naphthalenethiol, 4-nitro-1-naphthylamine (4—5%), and sulphur.
1 : 5-	5-Nitro-1-naphthylamine (55—58%); remainder was mainly 5-nitro-1-naphthalenethiol (oxidised to 5 : 5′-*dinitro*-1 : 1′-*dinaphthyl disulphide*; converted into 5-*nitro*-1-*naphthyl thiolacetate*).
1 : 6-	5-Nitro-2-naphthylamine (60—62%); remainder mainly 5-nitro-2-naphthalenethiol (converted into 5-*nitro*-2-*naphthyl thiolacetate*).
1 : 8-	The filtered solution, after reaction with insufficient reagent, exhibited the oxidation behaviour of a thiol, which computation indicated to be present (agreement within 5%).
2 : 7-	7-Nitro-2-naphthylamine (80%); remainder mercaptan, as indicated by oxidation to 7 : 7′-*dinitro*-2 : 2′-*dinaphthyl disulphide* and confirmed by computation.

The relative ease of amine-formation, *viz.*, 2 : 7- > 1 : 6- > 1 : 5- > 1 : 4- > 1 : 2-, is in accord with the theory of Hodgson (*J. Soc. Dyers and Col.*, 1943, **59**, 246; cf. Hodgson and Turner, *J.*, 1943, 318) that the reduction of the nitro-group by alkali sulphides is to be regarded as oxidation of the sulphide by the nitro-group; consequently the isomers capable of resonance into quinonoid forms, *viz.*, the 1 : 5-, 1 : 4-, and 1 : 2-dinitronaphthalenes, are in the order of increasing restraint due to the ease of mutual interaction between the nitro-groups, but the 2 : 7-, 1 : 3-, and 1 : 6-dinitronaphthalenes are in the decreasing order of independent easy resonance, since a β-group exceeds an α-group in this respect. The oxidising power of any particular nitro-group will be enhanced by its freedom from restraint and its ease of resonance.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

General Procedure.—A stirred solution or suspension of the dinitronaphthalene (10 g.) in methanol (80 c.c.), heated on the water-bath under reflux, is treated dropwise during *ca.* 15 minutes with a solution of sodium hydrogen sulphide. This solution, henceforward styled the "reagent," is prepared by treating 13% aqueous sodium sulphide (100 c.c.) with sodium hydrogen carbonate (14 g.) and then adding methanol (100 c.c.), filtering, and washing the residue on the filter with methanol, to afford a reagent (*ca.* 250 c.c.) containing sodium hydrogen sulphide (3·6—3·7 g. per 100 c.c.). After heating

the reaction mixture for a further 15 minutes (25 minutes for the 2 : 7-isomer), ice is added to the hot solution which is then poured into ice-water (*ca.* 1 l.); the mixture is filtered rapidly, and the residue washed with water and extracted with boiling 8—10% hydrochloric acid to dissolve out the nitronaphthylamine. The insoluble residue contains unchanged dinitro-compound and aromatic sulphides. It is important that the " reagent " be added until present in permanent (calculated) excess, the amount required varying according to the compound examined.

Dinitronaphthalenes.

1 : 2-*Dinitronaphthalene.*—(*a*) The compound (2·5 g.) in methanol (20 c.c.) was treated with the reagent (1·5 g.-mols.) during 10 minutes; the red colour, at first transitory, became permanent when *ca.* half of the reagent had been added. On dilution as above 2 : 2′-dinitro-1 : 1′-dinaphthyl sulphide (0·75 g.) was precipitated, filtered off, and crystallised from hot glacial acetic acid; pale yellow parallelepipeds, m. p. and mixed m. p. 204° (Hodgson and Leigh, *J.*, 1937, 1352, give m. p. 205°; Hoogeveen, *Rec. Trav. chim.*, 1901, **20**, 141, gives m. p. 204°) (Found: S, 8·7. Calc. for $C_{20}H_{12}O_4N_2S$: S, 8·5%). A specimen prepared from the sodium salt of 2-nitro-1-naphthalenethiol and 1-chloro-2-nitronaphthalene had m. p. 207°. The filtrate from the reduction, when treated with acetic acid, afforded bright yellow 2-nitro-1-naphthalenethiol, m. p. 205°; this dissolved readily in 3% aqueous sodium hydroxide or sodium carbonate, to give a solution which was more stable in air than the corresponding solutions from 1 : 5- and 1 : 6-dinitronaphthalenethiol; when stirred with excess of acetic anhydride and then kept overnight, it yielded a precipitate of 2-*nitro*-1-*naphthyl thiolacetate* which separated from 50% aqueous acetic acid in almost colourless crystals, m. p. 103° (Found: S, 12·8. $C_{12}H_9O_3NS$ requires S, 12·9%); a sample prepared from 1-chloro-2-nitronaphthalene had m. p. and mixed m. p. 102°. No amine formation could be detected.

(*b*) With quantities as in (*a*) but 0·75 g.-mol. of the reagent, the monosulphide (1·75 g.) was isolated, and there was a negligible amount of mercaptan.

(*c*) A solution of 1-chloro-2-nitronaphthalene (2 g.) in methanol (30 c.c.) was heated under reflux with the reagent (16 c.c.) for 30 minutes, the mixture worked up as in (*a*), and the considerable amount of mercaptan formed was converted into the acetyl derivative.

(*d*) 1 : 2-Dinitronaphthalene (0·5 g.) in methanol (10 c.c.) was treated dropwise during 5 minutes with sodium disulphide (0·5 g.-mol.) in water (8 c.c.); the initial red colour gave place to a yellow precipitate (0·4 g.) of crude 2 : 2′-dinitrodinaphthyl sulphide, m. p. 185—193°, containing sulphur.

1 : 4-*Dinitronaphthalene.*—From this compound (1·0 g.-mol.) and the reagent (0·5 g.-mol.), the product was 4 : 4′-dinitro-1 : 1′-dinaphthyl sulphide (identified by comparison with an authentic specimen), but from 1·0 g.-mol. of the reagent the main product was 4-nitro-1-naphthalenethiol with *ca.* 4—5% of 4-nitro-1-naphthylamine. Reduction with sodium disulphide appeared to form first the mercaptan and then the monosulphide, but all the products were so contaminated with sulphur that attempts at purification were frustrated.

1 : 5-*Dinitronaphthalene.*—The procedure used in (*a*) above gave 5-nitro-1-naphthylamine (55—58%). 5-*Nitro*-1-*naphthyl thiolacetate*, prepared from the alkaline filtrate by precipitating the orange-red 5-nitro-1-naphthalenethiol with acetic acid and subsequently acetylating its sodium salt, crystallised from boiling glacial acetic acid in pale yellow hair-like needles, m. p. 181—182° (Found: S, 12·7. $C_{12}H_9O_3NS$ requires S, 12·95%), which were readily soluble in cold acetone and moderately soluble in hot glacial acetic acid, but only slightly soluble in either hot or cold ethanol. 5 : 5′-*Dinitro*-1 : 1′-*dinaphthyl disulphide*, obtained by aërial or potassium ferricyanide oxidation of an alkaline solution of the above thiol, separated from boiling glacial acetic acid in small yellow crystals, m. p. 231—233° (Found: S, 15·6. $C_{20}H_{12}O_4N_2S_2$ requires S, 15·7%). The product formed by heating a mixture of 1-chloro-5-nitronaphthalene with sodium disulphide [prepared by dissolution together of sodium monosulphide nonahydrate (3 g.) and sulphur (0·5 g.)] in boiling ethanol for 8 hours afforded, after repeated extraction with boiling ethanol, a crystalline product, m. p. 190—230° (Found: S, 17·6%), which on further crystallisation melted sharply at 198° (Found: S, 18·2%); when the reduction was carried out in acetone by the general procedure, the final liquor had a very dark reddish-brown colour, and the yield of 5-nitro-1-naphthylamine decreased to 40%.

1 : 6-*Dinitronaphthalene.*—The main product was 5-nitro-2-naphthylamine (60—62%). 5-*Nitro*-2-*naphthyl thiolacetate*, obtained from the yellow 5-nitro-2-naphthalenethiol, crystallised from hot 50% aqueous acetic acid in pale yellow plates, m. p. 193—196° (Found: S, 12·7. $C_{12}H_9O_3NS$ requires S, 12·9%). When 1-chloro-6-nitronaphtbalene was heated under reflux in ethanol with sodium disulphide for 8 hours, the yield of sulphur compounds was negligible.

1 : 8-*Dinitronaphthalene.*—The violet solution, obtained when insufficient of the reagent was used and the excess of 1 : 8-dinitronaphthalene filtered off, oxidised rapidly in the cold, either in air or with potassium ferricyanide, and was decolorised by acetic acid with production of a gelatinous precipitate. These reactions would appear to indicate replacement of a nitro- by the SNa-group.

2 : 7-*Dinitronaphthalene.*—The main product was 7-nitro-2-napbthylamine (80%); the violet filtrate obtained by the general procedure afforded 7 : 7′-*dinitro*-2 : 2′-*dinaphthyl disulphide* on oxidation with potassium ferricyanide; this disulphide separated from boiling acetic acid in reddish-orange crystals, m. p. 264—265° (Found: S, 15·75. $C_{20}H_{12}O_4N_4S_2$ requires S, 15·7%). The acetyl derivative of the thiol, obtained as above, contained some dark green substance which could not be entirely removed by repeated crystallisation from acetic acid (charcoal); the crude 7-nitro-2-naphthyl thiolacetate had m. p. 185°, but the sulphur content was low and indicated that the admixed impurity did not contain sulphur.

Miscellaneous Reductions.

α-*Nitronaphthalene.*—(*a*) When treated by the Hodgson–Birtwell reagent (*loc. cit.*), this (2·5 g.) reacted slowly in the cold. (*b*) When heated under reflux with a slight excess of reagent for 2 hours, it (2·5 g.) gave α-naphthylamine (0·8 g., *ca.* 40%) and unchanged material (1·5 g.), but no sulphur dyes; α-naphthylhydroxylamine was probably also present. After longer heating with excess of reagent, the

yield of α-naphthylamine increased to *ca.* 75%, only 2—4% of unchanged material being recovered. (*c*) Treatment with aqueous sodium sulphide–sodium hydroxide at 90° for 3½ hours gave only indeterminate products.

β-Nitronaphthalene.—When treated as above, the β-isomer gave a small amount of β-naphthylamine and no sulphur dyes, but, since only a small amount of the initial substance remained unchanged, the reduction must have proceeded mainly to intermediate stages.

αα'-Azoxynaphthalene.—Prepared by the method of Cumming and Steel (*J.*, 1923, 2464), this was mainly unchanged by the Hodgson–Birtwell procedure, although a very small amount of α-naphthylamine was formed; similar non-reactivity was observed towards hot aqueous solutions of alkaline sodium sulphide.

α-Naphthylhydroxylamine.—Prepared according to the directions of Willstätter and Kubli (*Ber.*, 1908, **41**, 1936), this gave α-naphthylamine (50%) by the Hodgson–Birtwell procedure (*loc. cit.*).

β-Naphthylhydroxylamine.—Prepared as for the α-isomer (cf. also Baudisch and Furst, *Ber.*, 1917, **50**, 324) this afforded β-naphthylamine (50—55%) by the same method.

In the four preceding reactions some replacement of nitro- by SNa-groups occurs, since the filtered solutions give bright yellow precipitates on acidification; also, the solutions of the naphthylamines, obtained by steam-distillation of the acidified (acetic acid) reduction mixtures, when diazotised, afford intense green colours which indicate the presence of a volatile thiol and are due to nitroso-compound formation between the thiol and nitrous acid (cf. also Veselý and Chudozilov, *Rec. Trav. chim.*, 1925, **44**, 352).

1 : 3 : 8-*Trinitro- and* 1 : 3 : 6 : 8-*Tetra-nitronaphthalene.*—Reduction by the general procedure occurs rapidly, even in the cold, to give dark red solutions which contain sodium nitrite formed by displacement of nitro-groups. The filtrates, after separation of the insoluble material, were oxidised rapidly in air to give yellow products which, however, could not be purified.

Evidence for Thiol Formation by Calculation.—10 G. of a dinitronaphthalene requires 3·85 g. of NaSH for complete conversion into a nitronaphthylamine (8·624 g.), and 2·57 g. of NaSH for replacement of one nitro-group by SNa to give a nitronaphthalenethiol (9·42 g.).

1 : 6-Dinitronaphthalene (10 g.) was reduced by NaSH (3·5 g., determined by iodine titration) to give amine (minimum yield, 60%) and thiol (assumed 40% by difference). The amine would consume 2·31 g. of NaSH and the thiol 1·02 g., *i.e.*, a total of 3·32 g. If the real yield of amine (when loss incurred during manipulation and determination as azo-β-naphthol is taken into account) is assumed to be 65% and that of thiol 35%, the total NaSH required is 3·4 g. Since a slight excess of NaSH is always used in these reductions, the calculated and experimental results show reasonable agreement on the probable assumption that the thiol is substantially the only by-product formed.

1 : 5-Dinitronaphthalene (10 g.), yielding 55% of amine and 45% of thiol, similarly gives a calculated value of 3·3 g. of NaSH, compared with 3·5 g. actually used.

2 : 7-Dinitronaphthalene, yielding 80% of amine, gives a calculated value of 3·58 g. of NaSH used.

1 : 8-Dinitronaphthalene (10 g.) would require 2·57 g. for thiol replacement only; by using a deficiency of NaSH and basing calculations on the amount used, the agreement between the calculated and actual amounts was within 5%.

The authors are indebted to Imperial Chemical Industries Ltd. (Dyestuffs Division) for gifts of chemicals, and to The Department of Scientific and Industrial Research for a Senior Research Award (to E. R. W.).

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, October 1st*, 1948.]

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259. *Cation Exchange with a Synthetic Phenolsulphonate Resin. Part I. Equilibria with Univalent Cations.*

By T. R. E. KRESSMAN and J. A. KITCHENER.

A study has been made of the factors determining the position of equilibrium reached when a cation-exchange resin is placed in aqueous solutions of univalent metal salts. The sulphonate groups in the resin (the structure of which is discussed) are the only exchange groups operating below pH 8.

The equilibria are independent of concentration and largely of the anion. Exceptions which occur with Tl^+ and H^+ can be explained by incomplete dissociation. The equilibria are approximately represented by the law of mass action, and the equilibrium constants for Li^+, H^+, Na^+, K^+, Rb^+, and Cs^+ are a function of the hydrated ionic size expressed as the a° parameter of the Debye–Hückel theory.

The temperature coefficient of the K^+–H^+ system leads to the value of 1·95 kcals./g.-mol. for the heat of exchange; the free energy of exchange is 0·54 kcal./g.-mol. at 25°. The relatively large difference between these two values is interpreted as indicating that a change of hydration occurs when the cation passes from the solution to the solid phase.

Physical adsorption (as distinct from exchange) does not occur with highly dissociated neutral salts and acids, but becomes significant with chloroacetic acid.

SEVERAL approaches have been made to the physical chemistry of equilibrium cation exchange. Rothmund and Kornfeld (*Z. anorg. Chem.*, 1918, **103**, 129; 1919, **108**, 215) developed the empirical equation

$$(c_1/c_2)_{\text{solid}} = K(c_1/c_2)^p_{\text{soln.}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where c_1 and c_2 are the concentrations at equilibrium of the cations 1 and 2, and K and p are constants. Although this represents much of the data, it has no theoretical basis and has proved of little value in the development of the subject.

Other workers (*e.g.*, Ungerer, *Kolloid Z.*, 1925, **36**, 228; Renold, *Kolloid-Beih.*, 1935, **43**, 1) have represented the uptake of a particular ion A^+ from its solutions by a form of Freundlich adsorption isotherm. This view is equally empirical and neglects the behaviour of the other ion B^+. The two ions must play an equally important and symmetrical rôle in determining the final position of equilibrium.

A more acceptable treatment of ion exchange regarded as an adsorption process has been given by Boyd, Schubert, and Adamson (*J. Amer. Chem. Soc.*, 1947, **69**, 2818). This regards the cations A and B as competing for fixed separate sites in the solid, which are sufficiently far apart for the affinity per ion at every site to be the same and independent of the surrounding sites. Consequently, the system is formally analogous to Langmuir adsorption of a binary gas mixture, for which the adsorption isotherm is

$$(x/m)_{A^+} = kb_1[A^+]/(1 + b_1[A^+] + b_2[B^+]) \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $(x/m)_{A^+}$ is the amount of A^+ adsorbed per unit weight of adsorbent, $[A^+]$ and $[B^+]$ are the respective equilibrium concentrations of A^+ and B^+ in solution; and k, b_1, and b_2 are constants.

Yet another point of view regards ion exchange as a Donnan membrane equilibrium, since one set of ions—those of the solid—are prevented from diffusing by the nature of the material, while the other three ions in the system, A^+, B^+, and X^-, can diffuse freely. The equations of the Donnan equilibrium may, therefore, be applied immediately (Baumann and Eichhorn, *J. Amer. Chem. Soc.*, 1947, **69**, 2832).

The laws governing the equilibria in ion exchange can be treated equally well without recourse to any specific molecular theory by applying simple thermodynamics, *i.e.*, the exact form of the law of mass action, to the fundamental exchange equation:

$$R^-A^+ + B^+X^-, \text{aq.} \rightleftharpoons R^-B^+ + A^+X^-, \text{aq.} \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

which yields the equation:

$$a_{RB}a_{AX}/a_{RA}a_{BX} = K \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

It then remains to find expressions in practical terms for the various activities in the two phases. The relative activities of the two cations in the solid will be in the ratio of their concentrations provided the ionic sites in the solid are sufficiently far apart not to interact appreciably.

More generally, the activities could be replaced by products of concentration and activity coefficient. Because of the lack of data, however, most authors have used concentrations instead of activities in solution and have ignored entirely the possibility of non-ideality in the solid phase.

Preliminary Considerations.

Reversibility of the Equilibrium.—Renold (*loc. cit.*), using an aluminosilicate exchanger, found that different equilibrium positions were reached when approached from both sides, the tendency being to retain in the exchanger the ion with which it was originally saturated. Walton (*Trans. Illinois State Acad. Sci.*, 1941, **34**, No. 2, 124) showed that the graphs for the distribution ratios of calcium and sodium ions between a solution and a sulphonated-coal exchanger did not coincide when the equilibrium was approached from different sides. When the same sample of exchanger was again completely converted into the one form and the distribution ratios again determined, the graph lay between the original graphs. He concluded from this that the characteristics of the exchanger are conditioned by the ion with which it was last saturated and that after a number of conversions of the exchanger from one ion into the other it approaches a truly reversible state.

Experiments described later indicate that the equilibria studied in the present work (at least with univalent cations) are completely reversible.

Influence of the Anion.—Ungerer (*Z. Pflanz. Dung.*, 1930, **18**, *A*, 342; 1932, **23**, *A*, 353) in his study of the exchange of calcium aluminosilicate with the alkali-metal salts of a large number of anions, observed that the equilibrium position was a function of the anion. This was explained as a dehydration of the dissolved cations by the anions, with a resulting increased affinity of the exchanger for the smaller cation so produced. This, however, ignores the presence of the calcium ion and, furthermore, there is no independent evidence that the hydration of a cation in solution is in any way affected by that of the anion.

Ungerer's results are not in accordance with those of other workers. Thus, Patton and Ferguson (*Canadian J. Res.*, 1937, *B*, **15**, 103) found the same equilibrium position was obtained with a gel-type aluminosilicate exchanger in the sodium form and solutions of calcium nitrate and acetate; a slightly different one occurred with chloride. Ramann and Spengel (*Z. anorg. Chem.*, 1916, **95**, 115) observed the same equilibrium with chlorides, nitrates, and sulphates in the NH_4^+–Na^+, NH_4^+–K^+, and Na^+–K^+ systems.

The results of the present study (see below) also are not in keeping with those of Ungerer, but confirm those of Patton and Ferguson and of Ramann and Spengel. In addition, it will be shown in Part II (following paper) that the effect of the anion depends largely upon the valency of the cation involved.

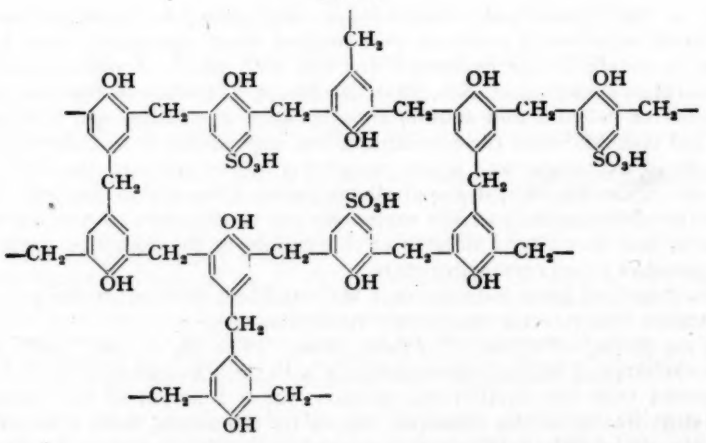
Choice of Ion-exchanger.—Many discrepancies appear in the literature of ion exchange, some of which have undoubtedly arisen because different workers have used different ion-exchange materials. The results obtained are greatly dependent upon the nature of the exchanger (Melsted and Bray, *Soil Sci.*, 1947, **63**, 209; Alexander, " Colloid Chemistry," VI, 1946, p. 201), a fact which has not been sufficiently recognised. It is accordingly important that the nature of the exchanger used should be defined as precisely as possible.

The modern synthetic resinous ion exchangers are, therefore, particularly suitable for fundamental studies, as a variety of structures can be built up and, in many, all the groups are freely accessible for exchange (in contrast to certain zeolites, cf. Patton and Ferguson, *loc. cit.*). In addition, an adequate knowledge of the molecular structure of the resin can generally be deduced.

The work described in this paper is concerned with the conditions prevailing when a synthetic resinous cation exchanger containing nuclear sulphonate groups is allowed to come to equilibrium with solutions of salts of univalent cations.

The resin is a cross-linked condensation product of formaldehyde with phenol and sodium phenolsulphonate (see Experimental), and the structure suggested by Houwink (*Trans. Faraday Soc.*, 1936, **32**, 125) can be accepted as its basic skeleton, although he has shown (" Physikalische Eigenschaften und Feinbau von Natur- und Kunstharzen," Leipzig, 1934) that no regular pattern exists in the molecule. However, if an attempt is made to prepare the sulphonate resin without the addition of the free phenol, no gel is obtained but merely a sticky semi-crystalline mass. It is therefore concluded that phenolsulphonic acid will not form cross links with formaldehyde in alkaline solution, only a low-molecular-weight lineate being formed. (This occurs only in alkaline solution: in acid solution an insoluble cross-linked product is obtained, a large number of $-CH_2-$ bridges being formed at the expense of the $-SO_3H$ groups, some of which are ejected as sulphuric acid.) Hence the three-dimensional cross links are evidently formed through the unsulphonated nuclei, the sulphonated nuclei being linked with two $-CH_2-$ bridges only. Houwink's diagrammatic structure must, therefore, be modified and the molecule will be of the form of Fig. 1.

FIG. 1.



By measuring the degree of sulphonation of the phenol during the preparation of the resin, the relative number of sulphonated and unsulphonated nuclei was found to be 5 : 7. The

monomeric weight, calculated from this ratio, is 1714. This weight contains five sulphonate groups and hence the equivalent weight of the resin, considered as a sulphonic acid, is 343. A direct determination of the total number of exchangeable hydrogen ions gave the value of 350. This same figure was obtained whatever the concentration of the salt solution and whatever the particle size of the resin grains. It was also independent of the salt used, whatever the anion and whatever the valency of the cation (at least up to a valency of 4), so long as the pH of the salt solution was below about 8. It is, therefore, considered that the figure truly represents the total number of exchangeable hydrogen ions attached to sulphonate groups.

A comparison of the measured equivalent weight with that calculated from the probable structure indicates that 97·5% of the calculated sulphonate groups are free for ion exchange. An independent check of this figure, by determination of the sulphur content of the resin by a combustion method, gave the figure 95·6%. The sulphur not in the form of sulphonate groups is probably present as sulphone links, while a small amount may exist as ester links ($-SO_3 \cdot CH_2-$).

The phenolic hydroxyl group, being weakly acidic, does not exchange ions except above about pH 10 and, since the whole of the present work is concerned with equilibria below pH 8, this group never comes into play, the SO_3^- group being the only active group operating.

Experimental.

Materials used.—The ion exchanger was prepared as follows. 1600 G. of phenol and 1600 g. of 98% sulphuric acid were mixed together and heated on a water-bath at 95° for 30 minutes. Sodium hydroxide solution (20%) was then added to neutralise the mixture, about 3500 ml. being required; a further 800 ml. were added as catalyst. To the solution were added 1600 g. of phenol and 1760 g. of paraform, together with 100 g. of sodium chloride which, in an unknown manner, renders the final resin much more easily granulated. The reaction mixture was evaporated until a gel was obtained, which was dried at 100° for 12 hours and then heated to 150° for 15 hours.

The resin was crushed to −10 mesh and soaked in water for about 15 minutes. The wet resin was then introduced into a glass tube of suitable size, in such a manner that no air bubbles were trapped between the particles. Hydrochloric acid (*ca.* 2N) was allowed to flow downwards through the column of resin at about 100 ml. per minute until the acidity of the effluent was the same as that of the influent. The resin was then washed with distilled water to remove excess of acid and the remains of a small amount of low-molecular-weight side products. To minimise any possible changes in the physical nature of the resin, it was air-dried at room temperature to a residual moisture content of about 25% only. The moisture content was accurately determined by drying a small sample to constant weight at 120° and was allowed for when weighing out the resin for the equilibrium measurements. The air-dried product was graded by sieving and stored in tightly stoppered bottles.

The non-volatile impurities in the hydrogen resin so prepared were determined by burning a sample in air: an ash of only 0·07% was obtained.

Stability of the Resin.—In the form of its metal salts the resin is quite stable, but in the presence of moisture the hydrogen form undergoes slow hydrolysis, and any but a freshly prepared sample contains traces of sulphuric acid. This effect is negligible for ordinary practical purposes, but it was considered desirable to eliminate it altogether for accurate work and, for this reason, the stable salt forms were always used as the starting points for those equilibrium measurements involving the hydrogen ion. This hydrolysis has been observed also in other synthetic organic exchangers containing nuclear sulphonic acid groups, including sulphonated coal, and the fact must be borne in mind when interpreting the results of previous workers.

Preparation of the Metal Forms of the Resin from the Hydrogen Form.—This was carried out by a method similar to that used for converting the crude resin into the hydrogen form. A glass tube of sufficient size to hold the desired quantity of resin was used, and a solution of a convenient neutral salt of the appropriate cation was allowed to flow over it until no more acid appeared in the effluent. The excess salt was washed off with water, and the resin air-dried to a residual moisture content of about 25%. The moisture content was determined as above.

Measurement of the Equivalent Weight.—The equivalent weight of the hydrogen resin considered as a sulphonic acid was measured by titrating the hydrogen ion displaced from a sample of the resin by an excess of sodium chloride, afterwards drying and weighing the sample.

About 6—8 g. of the air-dried resin were soaked in water and introduced into a small tube to form a column about 14 cm. high, and free from entrapped air bubbles. Any traces of acid were washed away by passing water downwards through the column. An approximately 0·25N-sodium chloride solution was then passed through the resin at a rate of 4—6 drops per second, and the effluent collected in approximately 100-ml. lots, which were titrated with N-sodium hydroxide. When no more acidity came away, the total volume of sodium hydroxide was noted, which represents the total replaceable hydrogen ions in the quantity of resin taken. No further acid was liberated when the resin was kept in contact with the sodium chloride solution overnight.

The resulting sodium resin was washed with water until free from chloride and dried at 120° to constant weight.

The methods used for determining the equivalent weights of the metal forms of the resin differed according to the particular metal ion in the resin. That of the ammonium form was measured by boiling an accurately weighed sample with sodium hydroxide solution and distilling the ammonia into standard acid. Ignition in oxygen of a weighed quantity of any of the alkaline-earth forms yielded a residue consisting of the pure sulphate, which was weighed. The tendency always, on ignition, is to form the pure sulphate; if, however, this is unstable then the residue was treated accordingly. Thus,

the aluminium form yielded the pure oxide, but certain of the forms containing other cations yielded residues of indefinite composition, which were then dissolved in acid and the cation determined by a standard procedure.

Ignition of the alkali-metal forms yielded the sulphates which, however, readily fused round the remaining resin and prevented complete combustion. The method employed here, therefore, was to convert the resin into the hydrogen form with an excess of hydrochloric acid, using the apparatus just described, and wash off the excess acid with water. The equivalent weight of the hydrogen form was then measured as previously described.

Preliminary Measurements of Velocity of Attainment of Equilibrium.—In order to determine how long was needed for equilibrium to be reached between a salt solution and the resin, some preliminary experiments were carried out of the rate of exchange in closed bottles with shaking at 25° ± 0·1°.

The system H-resin–KCl was chosen, and 10 milliequivs. of resin and 100 ml. of 0·1N-potassium chloride were used. (The use of the slightly unstable hydrogen form was justified here, since high accuracy was not required.) The resin was weighed into a 200-ml. stoppered bottle, and the potassium chloride introduced quickly by means of a pipette with a wide jet. Both the bottle and the chloride solution had previously been kept in a thermostat at 25°. The bottle was stoppered and shaken in the thermostat for 1 minute; the solution was then quickly decanted from the resin, and the acid produced as a result of the exchange was titrated in an aliquot portion of the solution with 0·1N-sodium hydroxide. This was repeated for different times up to 30 minutes. The final equilibrium value was obtained by shaking for 30 minutes and then allowing the system to stand at 25° for 3 days.

It was found that 90% of the equilibrium amount of acid was formed within 2·5 minutes with −10 + 20-mesh resin particles, and within 0·2 minute with −44 + 60-mesh particles. In each case 99% was obtained within 30 minutes (cf. Nachod and Wood, *J. Amer. Chem. Soc.*, 1944, **66**, 1380; Bauman, *Ind. Eng. Chem.*, 1946, **38**, 46). In the subsequent equilibrium measurements, periods many times longer than this were allowed, to ensure complete equilibrium. Large organic cations exchanged much more slowly and, here, duplicate samples of resin plus solution were left for different periods of time until identical results indicated that equilibrium had been reached.

Equilibrium Measurements.—A similar technique was used for the equilibrium determinations proper. Salt forms of the resin were always used because of the instability of the hydrogen resin. Generally NH_4^+ was used as the reference ion, for convenience of accurate analysis. The resin and the appropriate salt solution were introduced into a stoppered bottle in a thermostat at 25° and shaken manually at intervals during several hours. It was then left in the thermostat for several (usually 3—7) days. The solution was decanted from the resin, and an aliquot portion analysed for one of the ions involved in the exchange. Together with the number of exchangeable ions in the resin, and the quantity and concentration of the salt solution, sufficient data are available to calculate the equilibrium concentrations of both ions in both phases.

The same equilibrium position exactly was reached with all particle sizes of resin between 10 and 60 mesh, indicating that all the sulphonate groups are equally accessible to the exchanging cations.

Results.

Reversibility.—That the equilibria studied in the present work (at least with univalent cations) are completely reversible was demonstrated in an indirect manner by allowing various volumes of hydrochloric acid of known concentrations to come to equilibrium with known weights of potassium resin. The curve for the distribution of the ions between the resin and the solution was then plotted. Another series of equilibrium measurements was made by allowing samples of potassium resin to come to equilibrium with the acid and, when equilibrium had been attained, it was pushed back by the addition of known amounts of potassium chloride (*i.e.*, one of the products of the reaction) of the same concentration as the original hydrochloric acid, and the system again allowed to come to equilibrium. The distribution of the ions between the two phases was plotted on the same axes as before. Fig. 2 shows that the points lie exactly on the curve obtained without the addition of potassium chloride.

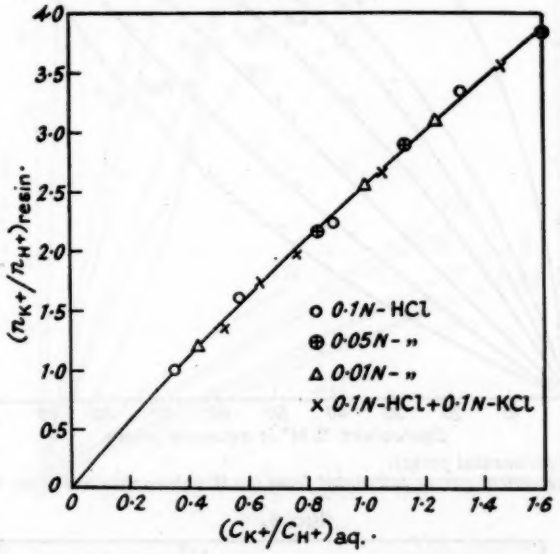
Effect of Concentration.—Fig. 2 shows also that the same equilibrium position is attained whatever the concentration of the ions in solution. This agrees with the findings of other workers for univalent cations on aluminosilicate exchangers (*e.g.*, Wiegner and Muller, *Z. Pflanz. Dung.*, 1929, **14**, *A*, **327**; Ivanov and Gapon, *J. Physical Chem., Russia*, 1941, **15**, 659). This is observed only with cations of equal valency: dilution of a system containing ions of different valency causes the ion of higher valency to pass into the solid phase. This behaviour is an attribute of the two-phase system involved, as has been shown mathematically by Ivanov and Gapon (*loc. cit.*).

Influence of the Anion.—The NH_4^+–K^+ system gave identical positions of equilibrium with the anions: Cl', NO_3', SO_4'', ClO_3', H_2PO_4', $Fe(CN)_6''''$, $Fe(CN)_6''''$, $H{\cdot}CO_2'$, $C_6H_5{\cdot}SO_3'$, I', $(COO)_2''$. The NH_4^+–Tl^+ system, on the other hand, gave a different position of equilibrium in nitrate solution from that in sulphate: the equilibrium constants are 12·7 and 9·2 respectively (see Fig. 4 and table). Thallous salts are well known to show incomplete dissociation (see, *e.g.*, Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," 1943, p. 396) and, in general, bivalent anions lead to a lower dissociation than univalent. This fact provides a satisfactory explanation of the results.

It is now recognised that many of the simple alkali-metal salts also are not entirely dissociated in solution (see, *e.g.*, Harned and Owen, *op. cit.*, pp. 145 *et seq.*); but the dissociation is sufficiently high and that of ammonium salts is sufficiently similar to that of the corresponding alkali-metal salts, that no significant difference is observed in the position of equilibrium as the anion is changed.

An extreme effect of low salt dissociation will be dealt with in detail in Part II, where it will be shown that scarcely any mercuric ion will pass into the solid phase from a solution of mercuric chloride.

FIG. 2.



Certain apparent exceptions in the NH_4^+–K^+ system should be mentioned. The following anions resulted in slightly different positions of equilibrium: $C_6H_5{\cdot}CO_2'$, $CH_3{\cdot}CO_2'$, HSO_4', hydrogen phthalate. With the exception of the last two there is no obvious reason for the different behaviour of these anions. The similarity in structure of benzoate to benzenesulphonate ion (which latter leads to a normal equilibrium), and of acetate to formate (which also behaves normally), would seem to preclude differences in dissociation of the salts.

It is likely that an exchange of the hydrogen ion also occurs to a certain extent with hydrogen phthalate, thus confusing the issue. This is certainly so with the HSO_4' ion, where a considerable exchange of hydrogen ion occurs:

$$NH_4R + KHSO_4 \rightleftharpoons HR + NH_4KSO_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

in addition to:

$$NH_4R + KHSO_4 \rightleftharpoons KR + NH_4HSO_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Equilibria among Univalent Cations.—To compare the affinity of the resin for univalent cations, equilibrium measurements were carried out with the ammonium form of the resin and solutions of the appropriate metal salt. (The hydrogen form was avoided for the reason already mentioned.) The chlorides of the alkali metals, the nitrate of silver, and the nitrate and sulphate of thallium were used.

In Fig. 3 the equivalent percentage of the univalent ion in the resin phase is plotted against that in the aqueous phase. The equivalent percentage is defined as follows:

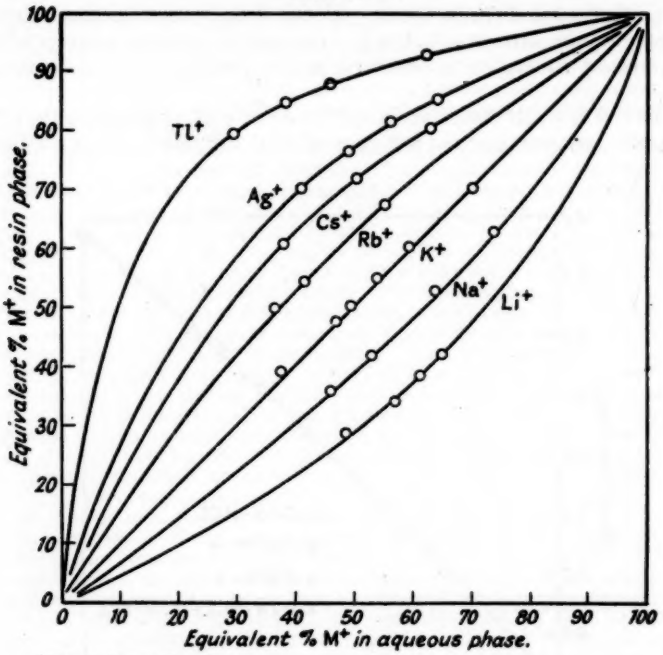
$$\text{Equivalent \% } M^+ \text{ in resin phase} = \frac{100\ (\text{meq. MR})}{\text{Total meq. resin}} = \frac{100\ (\text{meq. MR})}{\text{meq. MR} + \text{meq. } NH_4R} \quad . \quad . \quad . \quad (7)$$

$$\text{Equivalent \% } M^+ \text{ in aqueous phase} = \frac{100\ (\text{meq. } M^+)}{\text{Total meq. salt}} = \frac{100\ (\text{meq. } M^+)}{\text{meq. } M^+ + \text{meq. } NH_4^+} \quad . \quad . \quad . \quad . \quad (8)$$

This method of plotting has the advantage that the equilibrium positions of all ions, whatever the valency, can be plotted on the same axes, thus giving a direct comparison of their affinities.

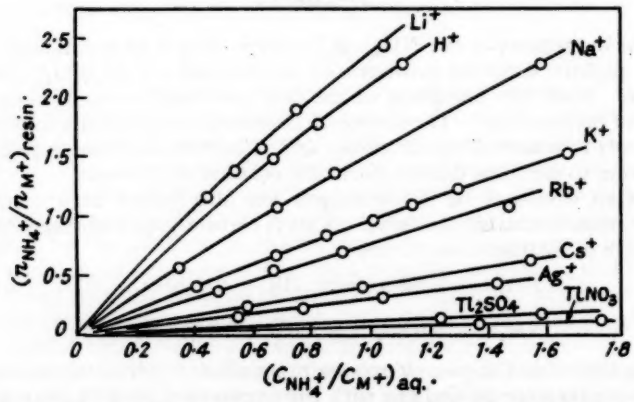
The method is less suitable, however, when it is desired to obtain a quantitative correlation between the equilibrium positions within a series of ions of the same valency. For this purpose

FIG. 3.



○ *Experimental points.*
— *Theoretical curves calculated from the* K *values obtained from Fig.* 4.

FIG. 4.



it is better to use the mass-action functions, from which the equilibrium constant can be calculated. For the equilibria involving the NH_4^+ ion and univalent cations

$$NH_4R + M^+, \text{aq.} \rightleftharpoons MR + NH_4^+, \text{aq.} \quad \ldots\ldots\ldots \quad (9)$$

the stoicheiometric equilibrium constant is given by

$$K = \frac{C_{M^+,\text{res.}} \cdot C_{NH_4^+,\text{aq.}}}{C_{NH_4^+,\text{res.}} \cdot C_{M^+,\text{aq.}}} = \left(\frac{C_{NH_4^+}}{C_{M^+}}\right)_{\text{aq.}} \Big/ \left(\frac{C_{NH_4^+}}{C_{M^+}}\right)_{\text{res.}} \quad \ldots\ldots\ldots \quad (10)$$

and will be obtained from the graph of

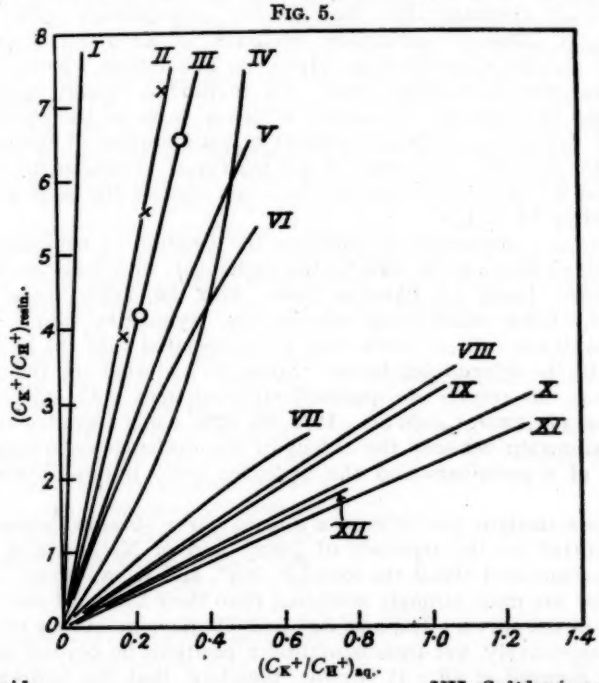
$$(C_{NH_4^+}/C_{M^+})_{\text{aq.}} \text{ against } (C_{NH_4^+}/C_{M^+})_{\text{res.}}$$

as plotted in Fig. 4. (The concentration of each cation in the solid phase is expressed as the number of equivs. of the cation to the total number of equivs. of cations in that phase. It is expressed in the aqueous phase as equivs. per l.)

Approximately straight lines are obtained, although a significant curvature does exist which appears to decrease with increasing affinity between the resin and the ion, *i.e.*, decreasing from

lithium to thallium. However, the curves cover a progressively smaller range of composition of the resin phase in this order, and, if they were all extended to cover the same range, the departure from linearity would probably be of the same relative magnitude in each case.

FIG. 5.



I, *Acetic acid.*
II, *Monochloroacetic acid*, 0·1N (*corr.*).
III, ,, ,, 0·05N (*corr.*).
IV, *Oxalic acid.*
V, *Monochloroacetic acid*, 0·05N (*uncorr.*).
VI, ,, ,, 0·1N (*uncorr.*).
VII, *Sulphuric acid.*
VIII, *Hydrochloric acid*, 1·5°.
IX, *Dichloroacetic acid.*
X, *Hydrochloric acid* 25°.
XI, ,, ,, 40°.
XII, *Trichloroacetic acid.*

All at 25° unless otherwise stated.

The curvature of the lines is not so great, however, as to preclude either a mean value or the limiting value of the slope being used to calculate the equilibrium constant. The departure from constancy is at the most only a few units %. The table shows the mean values of the stoicheiometric equilibrium constants at 25° for the equilibria against NH_4^+ obtained from Fig. 4.

A series of curves illustrating the equilibria between a potassium resin and solutions of acids having various dissociation constants is shown in Fig. 5.

Exchange equilibrium constants and ionic sizes.

Cation.	Equilm. const. against NH_4^+ at 25°.	a°. Chlorides. Harned & Owen.	a°. Chlorides. Stokes & Robinson.	a°. Nitrates. Harned & Owen.	Crystal radius, A.*	Hydrated radius, A., from mobility.†
Li^+	0·40	5·56	4·32	5·23	0·60	2·31
H^+	0·47	5·60	4·47	—	—	—
Na^+	0·67	4·49	3·97	3·15	0·95	1·78
K^+	1·05	3·86	3·63	1·77	1·33	1·22
NH_4^+	1·00	(1·81)	—	—	1·48	1·21
Rb^+	1·70	3·50	3·49	1·63	1·48	1·18
Cs^+	2·40	2·97	—	1·54	1·69	1·16
Ag^+	3·20	—	—	2·0	1·26	1·45
Tl_2SO_4	9·2	—	—	—	1·44	1·20
$TlNO_3$	12·7					

* The crystal radii are from Pauling (" The Nature of the Chemical Bond," 1944, p. 346).

† The hydrated radii are calculated from the equation given by Walden (" Elektrochemie nichtwässriger Losungen," 1924, p. 189), using the mobility figures quoted in Landolt-Börnstein's Tabellen, Ergänzungsband IIIc, 2059 (1936).

DISCUSSION.

Relative Ion–Resin Affinities.—From the equilibrium constants given in the table the approximate equilibrium constant for any pair of the ions can be calculated. Thus the equilibrium constant for the K^+–Rb^+ equilibrium will be approximately $(K_{NH_4^+/K^+})/(K_{NH_4^+/Rb^+})$. This is sufficiently accurate to allow an estimate to be made of the separation of univalent cations from admixture in solution, which might be effected by an exchanger of the phenolsulphonate type. The method is equally applicable to mixtures containing more than two cations. However, a precise value of the equilibrium constant in any particular case cannot be predicted without a consideration of the specific influence of individual ions on the activity coefficients of salt mixtures. Thus, in the example above, the activity coefficient of K^+ in the presence of Rb^+ is not exactly the same as in the presence of the same concentration of NH_4^+.

Various workers have attempted to correlate the position of equilibrium, which gives a measure of the relative affinity of the ions for the exchanger, with other known and measurable properties of the ions. Jenny (*J. Physical Chem.*, 1932, **36**, 2217), using an aluminosilicate exchanger, obtained a linear relationship between his "symmetry value" and the reciprocal of the crystal radius of the cation. However, he appreciated that the hydrated and not the crystal radius must be the determining factor. Since the hydrated and the crystal radii change in opposite directions, his results are qualitatively consistent with this concept.

Nachod and Wood (*J. Amer. Chem. Soc.*, 1945, **67**, 629), using a sulphonated-coal exchanger, found a linear relationship between the extent of the exchange occurring in an arbitrarily standardised series of experiments and the hydrated ionic radius obtained from mobility measurements.

In neither case is a straight line or even a smooth curve obtained when the results of the present work are plotted by the methods of Jenny and of Nachod and Wood (cf. table). By the method of Nachod and Wood the ions Li^+, Na^+, and K^+ are found to lie on a straight line, but Rb^+ and Cs^+ are more strongly attracted than their hydrated radii require, and they cause a sharp break in the curve. The ions Ag^+ and Tl^+ have mobilities between Na^+ and K^+ and K^+ and Rb^+, respectively, yet their equilibrium positions lie beyond that of Cs^+, so that these do not lie on a curve at all. It is clear, therefore, that the hydrated ionic radius as determined from mobility measurements is not the determining factor.

Recently Boyd, Schubert, and Adamson (*ibid.*, 1947, **69**, 2818) studied the equilibrium conditions in a phenol sulphonate resin exchanger, Amberlite IR-1. This apparently carries $-CH_2 \cdot SO_3^-$ exchange groups similar to, though not identical with, the nuclear $-SO_3^-$ groups in the exchanger used in the present work. These authors used the "distance of closest approach" $a°$ of the Debye–Hückel equation

$$-\log \gamma_{\pm} = A\sqrt{\mu}/(1 + Ba°\sqrt{\mu}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

as an index of ionic size, and they plotted the reciprocal $1/a°$ against the standard free energy of formation of the metal-resin salt obtained from the equilibrium constant K:

$$-\Delta G°_{MR} = RT \log_e K \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

A straight line was drawn through the points, suggesting that $a°$ is the factor determining the affinity.

Unfortunately, several unsatisfactory features mar the validity of this work. First, lithium appears to have been plotted with the erroneous value for $-\Delta G°_{MR}$ of $+60$, whereas their Table VII gives it as -60: the latter figure is obviously the correct one, since it is consistent with other data in the paper. Secondly, the $a°$ value used for sodium is quoted from Brown and MacInnes (*J. Amer. Chem. Soc.*, 1935, **57**, 1357) as 5·2, instead of 4·45. Thirdly, there appears to be an arithmetical error in the calculation of $a°$ for ammonium chloride from the data quoted by Latimer ("The Oxidation States of the Elements"): a re-calculation gives a value of about 2 instead of 4·5. However, the activity data on ammonium chloride are too sparse to provide a satisfactory basis for calculation and it is probably advisable to omit NH_4^+ from the discussion altogether.

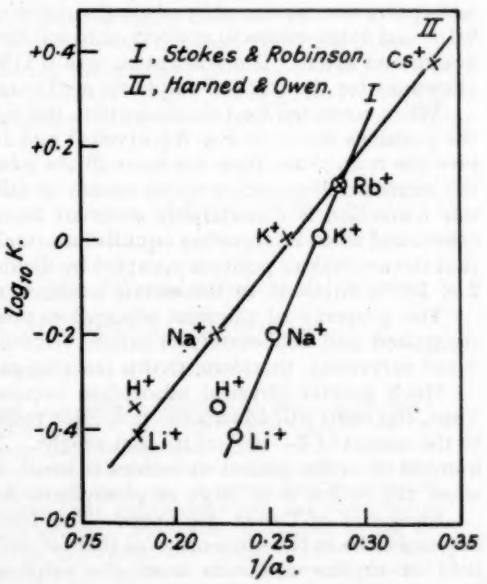
When these discrepancies are corrected, the points no longer lie on a straight line, but do lie roughly on a smooth curve. The equilibrium constants for H^+ and the alkali-metal ions in the present work, when similarly plotted with the same $a°$ values, give a curve of the same type. This conception of using the distance of closest approach to correlate affinities appears, therefore, to be an improvement on that of crystal or hydrated radii.

The utility of the method is restricted, however, by the incompleteness as well as by the uncertainty of much of the existing activity data, especially as the value of $a°$ is very sensitive to small differences in activity coefficients. In addition, $a°$ is not a fundamental constant, and the value obtained depends largely on the concentration at which equation (11) is applied.

In an attempt to test the idea further, $a°$ values have been calculated at 0·1N and 25° from activity data collected by Harned and Owen (*op. cit.*, pp. 547, 562—564) (see table). The incompleteness of the available data renders it impossible to include in one series all the cations studied. The chlorides of Li^+, Na^+, K^+, Rb^+, and Cs^+ yield $a°$ values which give a straight line when the reciprocals are plotted against log K, as Fig. 6 shows. The hydrogen ion lies slightly, but significantly, off the line in the direction indicating too high an affinity for its $a°$ value. This is clearly the effect of incomplete ionisation of the hydrogen resin considered as an acid. It is understandable, as potentiometric titrations indicate that the parent phenol- and cresol-sulphonic acids have dissociation constants of the order of 10^{-2}.

The only salt of silver for which an $a°$ value is obtainable is the nitrate. The calculation of $a°$ values for the alkali-metal nitrates should then enable silver to be included in the series. The values obtained are shown in the table. With the possible exception of Li^+ and Na^+, these are seen to be so low as to have no real significance, as the higher terms of the Debye–Hückel theory begin to have an influence (see MacInnes, "The Principles of Electrochemistry," 1939, p. 164) and, in addition, silver nitrate and the alkali nitrates are known to show abnormal behaviour in solution (*idem, ibid.*, pp. 164, 334). It is, therefore, at present impossible to draw any conclusions whatever in regard to silver. Similar difficulties exist with Tl^+ (see Harned and Owen, *op. cit.*, pp. 396, 397).

FIG. 6.



Stokes and Robinson (*J. Amer. Chem. Soc.*, 1948, **70**, 1870) have recently put forward a semi-empirical modification of the Debye–Hückel equation. Their $a°$ values, although limited to H^+, Li^+, Na^+, K^+, and Rb^+, are also found to yield a straight line when the reciprocals are plotted against log K as before, the point for the hydrogen ion again lying in a position indicating incomplete ionisation of the hydrogen resin (see table, and Fig. 6).

Summarising, the use of the $a°$ parameter appears to be a sound means of correlating the affinities of the univalent cations, but the lack of sufficient activity data and the limitations of the Debye–Hückel equation raise such serious restrictions that no satisfactory proof of the validity of the concept can be obtained at present.

Equilibria Involving the Hydrogen Ion.—It has long been recognised (Jenny, *J. Physical Chem.*, 1932, **36**, 2253; *Kolloidchem. Beih.*, 1927, **23**, 428; Wiegner, *J. Soc. Chem. Ind.*, 1931, **50**, 103T) that the general laws governing the exchange of metal ions, *i.e.*, in more or less neutral solution, do not apply when the hydrogen ion is involved.

Detailed discussions have hitherto been confined to inorganic aluminosilicate exchangers, and only one brief mention of the subject has been made from the standpoint of the organic cation exchangers (Boyd, Schubert, and Adamson, *loc. cit.*, p. 2829).

It is obvious from the literature and the results of the present work that the two types of exchanger behave differently towards the hydrogen ion. Jenny (*loc. cit.*, 1927) showed that the hydrogen ion is more strongly held by a zeolite than any of the other univalent ions, the series for chlorides being $H > Cs > Rb > NH_4 > K > Na > Li$. The hydrogen ion, under the same conditions, shows a comparatively feeble affinity for organic exchangers containing sulphonic groups, the series being (see Fig. 4) $Li < H < Na < (K, NH_4) < Rb < Cs$. This is the same position as found by Boyd, Schubert, and Adamson (*loc. cit.*) for the methylenesulphonic acid exchanger used by them.

This low affinity indicates that it is the hydrated radius of the ion, like that of the metal

cations, which is the determining factor, and both forms of the resin can be regarded as largely ionised, though not dissociated.

The high affinity of the hydrogen ion for the zeolites, on the other hand, must be regarded as the result of the capacity of the >Al·O– group to form the covalently linked >Al·OH group. Accordingly, the zeolite behaves as a weak acid, while the resin sulphonic acid behaves as a strong acid.

From this point of view, the equilibrium

$$\text{K-exchanger} + \text{HA} \rightleftharpoons \text{H-exchanger} + \text{KA} \quad . \quad . \quad . \quad . \quad . \quad (13)$$

(where HA is the acid in the aqueous solution) is seen to be analogous with the competition of two acids for the same base: when H-exchanger is the weaker acid the equilibrium lies to the right, and *vice versa*. This is exemplified by the curves of Fig. 5.

The amount of exchange occurring with the stronger acids, *e.g.*, hydrochloric, sulphuric, dichloroacetic, is in each case the same at 0·1N and at 0·05N, but increased dilution of monochloroacetic acid appears to cause *less* hydrogen ion to pass into the resin phase (Fig. 5, curves V and VI). This behaviour is not in accord with the law of mass action, nor can it be explained by dissociation (which would have the opposite effect). It has been found to be due to physical adsorption of the undissociated molecules of the weak acid on the resin. This adsorption was measured by placing samples of hydrogen resin in contact with known volumes of 0·1N- and 0·05N-monochloroacetic acid solutions and titrating the acidity of the aqueous solution before and after. The adsorption was 0·113 and 0·0604 milliequiv. per g., respectively, after allowance for the trace of sulphuric acid coming from the hydrogen resin, already referred to.

When corrected for this adsorption, the equilibrium curves for monochloroacetic acid occupy the positions shown in Fig. 5 (curves II and III). It is seen that *more* hydrogen ion now passes into the resin phase from the more dilute solution than from the less dilute, in accordance with the increased dissociation which occurs on dilution. The true equilibrium position obtained by this correction is considerably different from the apparent one, and this must obviously be considered when interpreting equilibrium results involving weak acids. It is likely, for example, that the anomalous position occupied by dichloro- and trichloro-acetic acids ($K_a = 5 \times 10^{-2}$ and 2×10^{-1}), adjacent to the strong acids, is a result of this effect.

The property of physical adsorption possessed by synthetic resin gels has already been recognised and deliberately enhanced (Dutch Patent 59,449; Brit. Pat. Appl. 29,197/45). It is not surprising, therefore, that a resinous cation exchanger should possess the same property.

Much greater physical adsorption occurs when large unionised molecules are involved. Thus, the resin will adsorb the non-ionic molecules of the wetting agent " Lissapol N " (I.C.I.) to the extent of 5—10% of its own weight. No adsorption occurs with strong acids, where the number of undissociated molecules is small, or with the highly dissociated neutral salts, even when the cation is as large as phenylbenzyldimethylammonium (see Part III).

Energetics of Cation Exchange.—The fact that the affinity of different univalent cations appears to be in the same order as their a° parameters might be taken to mean that the ions are held at similar distances from the sulphonate ion by purely Coulombic attraction and, consequently, the smaller the cation the greater the affinity, since the energy will be given by e^2/Da° (D is the dielectric constant). There can be little doubt that this concept (previously arrived at in a cruder form by Jenny and others) is broadly correct, but further consideration of the energy changes involved shows that the problem is more complex than this simple picture implies.

It is, unfortunately, very difficult to estimate accurately the interaction energy of two ions at their distance of closest approach. In addition to the Coulombic attraction, allowance ought to be made for the attraction due to mutual polarisation and the van der Waals forces and, in the opposite sense, for repulsive forces. As these factors cannot be assessed with any reliability, it is usual to neglect all three on the grounds that their net result, at least, may be small compared with the Coulomb energy.

There remains the difficulty that the dielectric constant of the medium near an ion is not that of the pure medium. Webb (*J. Amer. Chem. Soc.*, 1926, **48**, 2589) gives values of the " effective dielectric constant " at different distances from an ion. Extrapolating Webb's figures, the dielectric constant to be used for H^+ and K^+, whose chlorides * have a° values of 5·6 and 3·9 A., are 45 and 40 respectively, giving energies of Coulomb attraction of 1·30 kcals./g.-mol. for H^+ and 2·10 kcals./g.-mol. for K^+. Hence, the change of Coulomb

* Strictly an a° value for the cation-sulphonate contact should be used. However, this is not known and cannot be calculated, but that for the corresponding chloride will not be very different.

energy on replacing a potassium ion in the resin by a hydrogen ion is an absorption of 0·80 kcal./g.-mol.

These figures may be compared with the thermal data obtained from a study of the equilibrium

$$KR + HCl \rightleftharpoons HR + KCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

The equilibrium constant, defined by

$$K = [KCl][HR]/[HCl][KR] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

is found to have the values 0·30, 0·40, and 0·466 at 1·5°, 25·0° and 40·0°, respectively (see Fig. 5). Applying the van't Hoff isochore, the standard heat of reaction $\Delta H°$ is +1·95 kcals./g.-mol. The standard free energy of exchange $\Delta G°$ is given by $-\Delta G° = \boldsymbol{R}T \cdot \log_e K$, which yields a value of $+\Delta G° = +0·54$ kcal./g.-mol. at 25°. Hence, from the equation $\Delta G° = \Delta H° - T\Delta S°$, the value of $T\Delta S°$ is +1·41 kcals./g.-mol.

The entropy contribution is thus nearly as great as the heat of reaction, and of opposite sign, leading to a low value for the free energy of exchange. This indicates almost certainly that there is a change in the degree of hydration of the ions when they pass from the solution to the solid phase: a mere interchange of ions would not be accompanied by a change of entropy. Further, the calculated Coulomb energy of exchange (*viz.*, 0·80 kcal.) is only about half of the heat of exchange (1·95 kcals.). The rest of the latter probably comes from the heat of hydration. Judging by its position in the exchange series, H^+ is more hydrated than K^+; consequently, if some dehydration occurs when an ion is taken up during the reaction (14), there is likely to be a net *decrease* in the total amount of water bound by hydration. Hence, energy must be supplied, which will be a positive contribution to ΔH. This corresponds with the positive entropy change already found from the equilibrium data.

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260. *Cation Exchange with a Synthetic Phenolsulphonate Resin. Part II. Equilibria with Multivalent Cations.*

By T. R. E. Kressman and J. A. Kitchener.

The study described in Part I has been extended to equilibria between an ammonium resin and salts of Be^{++}, Mg^{++}, Ca^{++}, Sr^{++}, Ba^{++}, Cd^{++}, Cu^{++}, Zn^{++}, Co^{++}, Ni^{++}, Pb^{++}, Hg^{++}, Al^{+++}, Th^{++++}, Zr^{++++}. They obey the law of mass action, concentrations being used instead of activities. This is discussed in relation to activity coefficients in uni-bivalent salt mixtures.

All the sulphonate groups in the resin can be neutralised by an equivalent number of multivalent cations, and this leads to the hypothesis that multivalent ions are not closely associated with their valency number of sulphonate groups. Ionic size (measured by the $a°$ parameter) seems to be a factor determining the affinity of bivalent cations for the resin. These observations can be reconciled by the assumption that the cation is close to one sulphonate group and relatively far from the other. The generally increasing affinity observed with increasing valency is in keeping with this concept.

Incomplete dissociation of the salts of multivalent ions in solution is an important factor in determining the extent of exchange with these ions and gives an explanation also of the effect of the anion.

Part I (preceding paper) dealt with equilibria between a phenolsulphonic acid–formaldehyde resin and various simple univalent cations. The present paper is concerned with equilibria involving chiefly bivalent ions, and these were studied by the same experimental technique as that used in Part I. The ammonium ion was used as the reference ion in the resin, and the reactions are, therefore, of the type

$$2R^-NH_4^+ + M^{++}X^-_2, \text{aq.} \rightleftharpoons R^-_2M^{++} + 2NH_4^+X^-, \text{aq.} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

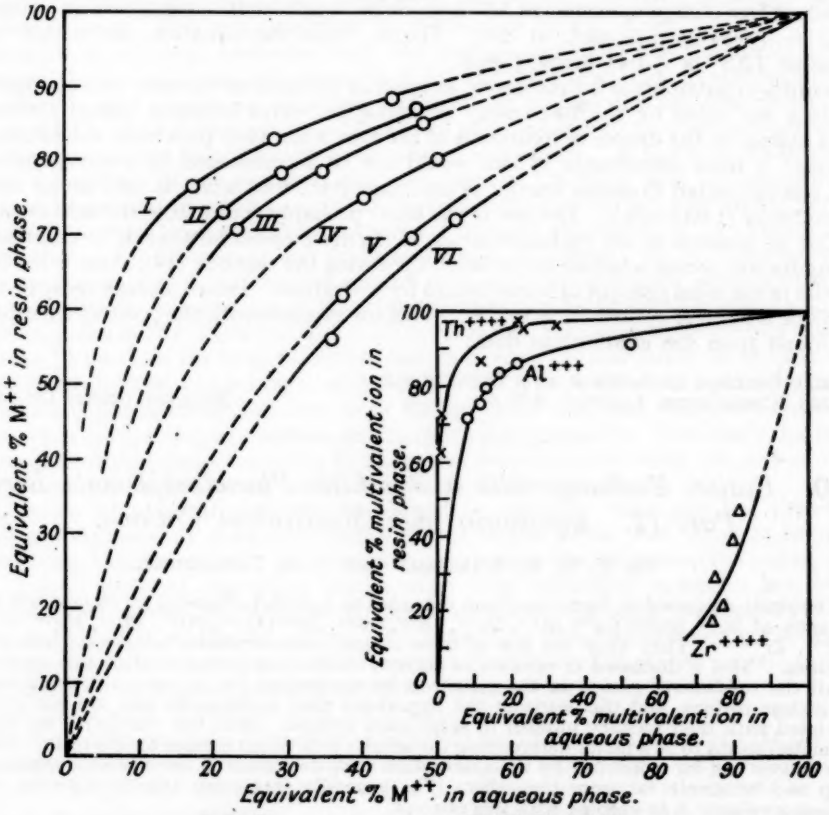
The results are plotted in terms of equivalent percentages in Fig. 1. As discussed in Part I, this method of plotting is the most suitable for comparing the affinities for the resin of ions of different valency, and a comparison of the curves with Fig. 3 of Part I shows clearly the generally higher affinity of the resin for the doubly charged ions than for the singly charged ones. There is, nevertheless, a certain overlap, and Tl^+, in spite of its single charge, is as strongly held to the resin as Ba^{++} in 0·1N-solution.

The curves of Fig. 3 in Part I are symmetrical in form while those of Fig. 1 are unsymmetrical.

This is a reflection of the symmetrical uni-univalent system and the unsymmetrical uni-bivalent system respectively.

The results expressed by Fig. 1 are in accord with the simple law of mass action using concentrations, as is illustrated by Fig. 2, where the appropriate mass-action functions are plotted. In this graph the concentration of each cation in the resin phase is expressed as the ratio of the number of equivalents of that cation to the total number of equivalents of cations in that phase; this ratio is dimensionless. The concentration of each cation in the aqueous phase is expressed as equivs. per l. Alternatively, it is sometimes convenient, especially when it is desired to compare the extent of exchange occurring in solutions of different concentrations,

FIG. 1.



I, $BaCl_2$
II, $SrCl_2$
III, $CaCl_2$
IV, $MgCl_2$; $ZnCl_2$
V, $BeSO_4$
VI, $CdCl_2$

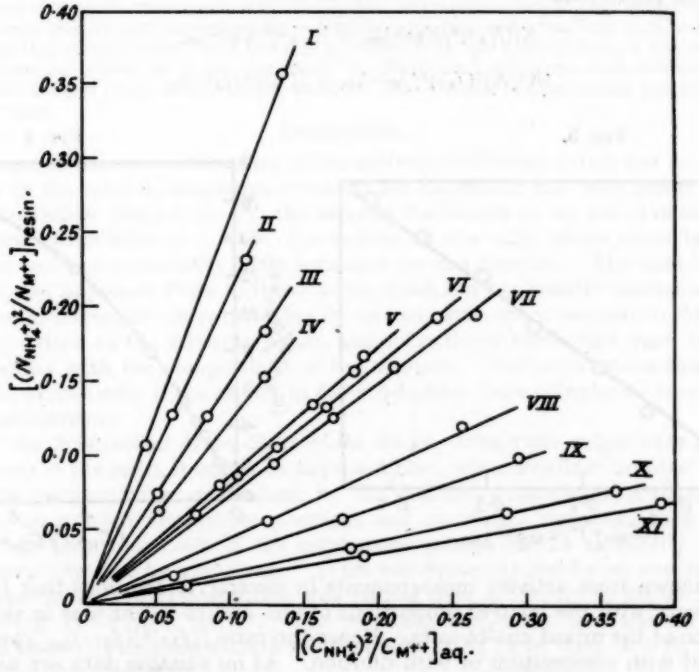
to express the aqueous concentration as a ratio in a manner identical with that used for the solid phase. The corresponding mass-action function, like that for the solid phase, is then dimensionless, and its numerical value will be v times that calculated by the first method (v is the volume of solution, in litres, containing 1 g.-equiv. of total cations or of the anion). The points relating to various initial concentrations of a given cation lie on a common curve in Fig. 2, but each concentration yields a separate curve when plotted by the alternative method. This is illustrated in Fig. 5. Thus a separate constant is obtained, from the slopes of the curves, for each concentration. It is proposed to call the constant so obtained the "exchange constant" and to designate it by K': like that obtained for ions of equal valency, it is dimensionless. The equilibrium constants, K, obtained from the slopes of the curves in Fig. 2 are the true stoicheiometric mass action constants and are independent of dilution. They have the dimensions of concentration and the values are given in the table, where

$$K = \left[\frac{(C_{NH_4^+})^2}{C_{M^{++}}}\right]_{aq.} \Big/ \left[\frac{(C_{NH_4^+})^2}{C_{M^{++}}}\right]_{res.} \quad \ldots\ldots\ldots\ldots \quad (2)$$

Equilibrium constants for the exchange between NH_4*-resin and various bivalent metal salts.*

Cation (and anion).	Concn. studied, N.	Equilm. constant at 25°.	Cation (and anion).	Concn. studied, N.	Equilm. constant at 25°.
Cd^{++} (chloride)	0·1	0·384	Cu^{++} (chloride)	0·1	1·23
Be^{++} (sulphate)	0·1	0·471	Ni^{++} ,,	0·1	1·23
Mg^{++} ,,	0·1—0·005	0·667	Co^{++} ,,	0·1	1·32
(formate)	0·1	0·912	Ca^{++} ,,	0·1	2·16
(chloride)	0·1—0·005	1·14	Sr^{++} ,,	0·1	3·00
Mn^{++} (sulphate)	0·1	0·82	Pb^{++} (nitrate)	0·1	4·65
(chloride)	0·1	1·00	Ba^{++} (chloride)	0·1	5·64
Zn^{++} ,,	0·1	1·14	Hg^{++} ,,	0·10; 0·05	0·038
UO_2^{++} (nitrate)	0·1	1·00			

FIG. 2.



I, $CdCl_2$.
II, $BeSO_4$.
III, $MgSO_4$.
IV, $MnSO_4$.
V, $MgCl_2$; $Mg(NO_3)_2$; $ZnCl_2$.
VI, $CuCl_2$; $NiCl_2$.
VII, $CoCl_2$.
VIII, $CaCl_2$.
IX, $SrCl_2$.
X, $Pb(NO_3)_2$.
XI, $BaCl_2$.

The range of variation in resin composition represented by the curves is relatively limited, owing to the strong affinity of the resin for the bivalent ions as compared with that of the reference ion NH_4^+. It is perhaps not surprising, therefore, that the law of mass action should apply over this rather narrow range. The graphs cannot accurately be extended beyond the range illustrated, since large proportions of resin to solution are needed and the experimental error is inevitably large. Nevertheless, by starting with a resin containing bivalent ions, *e.g.*, Mg^{++}, and allowing it to come to equilibrium with solution of ammonium chloride, the equilibrium was approached from the other side and the upper portions of the curve obtained by the use of a low ratio of solid to aqueous phase, thus permitting high accuracy to be achieved.

Fig. 3, obtained in this way, represents an overall variation in resin composition from 100 equivs. % of Mg^{++} to 40 equivs. %. The graph shows clearly that the law of mass action is obeyed over this wide range, and it is remarkable that such agreement should be obtained by the use of concentrations and not activities. This result has several important implications, as described below.

Influence of Activity Coefficients on Bivalent Salt Solutions.—Thermodynamically the following relationship must define the ion exchange equilibrium $2(A^+)_{res.} + B^{++}{}_{aq.} \rightleftharpoons B^{++}{}_{res.} + 2(A^+)_{aq.}$:

$$K^\circ\left[\frac{(a_{A^+})^2}{a_{B^{++}}}\right]_{resin} = \left[\frac{(a_{A^+})^2}{a_{B^{++}}}\right]_{aq.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

i.e.,

$$K^\circ\left[\frac{(N_{A^+})^2}{N_{B^{++}}}\right]_{res.}\left[\frac{(f_{A^+})^2}{f_{B^{++}}}\right]_{res.} = \left[\frac{(C_{A^+})^2}{C_{B^{++}}}\right]_{aq.}\left[\frac{(f_{A^+})^2}{f_{B^{++}}}\right]_{aq.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where K° is the thermodynamic equilibrium constant, N_{A^+} and $N_{B^{++}}$ are the ratios of the number of equivalents of the cations A^+ and B^{++} to the total number of equivalents of the cations in the resin phase, *i.e.*,

$$N_{A^+} = n_{A^+}/(n_{A^+} + n_{B^{++}}) \text{ and } N_{B^{++}} = n_{B^{++}}/(n_{A^+} + n_{B^{++}}) \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and C_{A^+} and $C_{B^{++}}$ are the concentrations of the two ions in the aqueous phase. Experimentally, the linear graphs prove that

$$K[(N_{A^+})^2/N_{B^{++}}]_{res.} = [(C_{A^+})^2/C_{B^{++}}]_{aq.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Hence

$$(K^\circ/K)[(f_{A^+})^2/f_{B^{++}}]_{res.} = [(f_{A^+})^2/f_{B^{++}}]_{aq.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

FIG. 3.

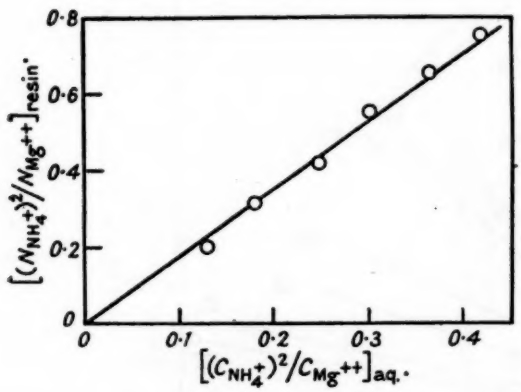
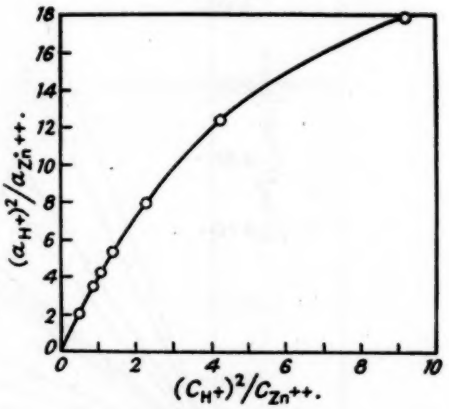


FIG. 4.



It is well known from activity measurements in electrolyte solutions that f_{A^+} and $f_{B^{++}}$ in solution must vary with the relative proportions of uni- and bi-valent ions in the solution and with the dilution of the mixed uni–bi-salts. Hence the ratio $[(f_{A^+})^2/(f_{B^{++}})]_{aq.}$ cannot in general remain constant with composition or with dilution. As no suitable data are available in the literature on this point, a series of measurements were carried out on the system $ZnCl_2$–HCl, using an e.m.f. method.

The activity ratios $(a_{H^+})^2/(a_{Zn^{++}})$ so obtained are plotted against the corresponding concentration ratios in Fig. 4: the graph is seen to be far from linear. It follows, therefore, that $[(f_{H^+})^2/f_{Zn^{++}}]_{aq.}$ changes over the range of composition involved.

At the same time, the equilibrium curve for the system Zn–resin–HCl, like that of the other uni-bivalent systems, is a straight line when plotted in terms of concentrations (see Fig. 5).

Therefore

$$[(f_{H^+})^2/f_{Zn^{++}}]_{aq.} = (K^\circ/K)[(f_{H^+})^2/f_{Zn^{++}}]_{resin} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

and, consequently, the changes occurring in $[(f_{H^+})^2/f_{Zn^{++}}]_{aq.}$ must be accompanied by proportionate changes in $[(f_{H^+})^2/f_{Zn^{++}}]_{resin}$.

EXPERIMENTAL.

Measurement of Activities in $ZnCl_2$–HCl *Mixtures.*—The following cell was used

$$Zn/Hg\ (2\ phase)\ |\ ZnCl_2\text{–}HCl,\ aq.\ |\ H_2\ (Pt) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

A two-phase zinc-amalgam electrode has been shown by Clayton and Vosburgh (*J. Amer. Chem. Soc.*, 1936, **58**, 2093) and by Cohen (*Z. physikal. Chem.*, 1900, **34**, 612) to behave exactly as a pure zinc electrode. The e.m.f. of the cell is accordingly:

$$E_{cell} = E_H - E_{Zn} = -E_{Zn/Zn^{++}} + (RT/2F)\log_e[(a_{H^+})^2/a_{Zn^{++}}] \quad . \quad . \quad . \quad . \quad (9)$$

Hence from measurements of the e.m.f. of the cell when the proportions of $ZnCl_2$ and HCl are varied, the total concentration being kept constant, the activity ratio $(a_{H^+})^2/(a_{Zn^{++}})$ corresponding to the known concentration ratio can be obtained. The value used for $E_{Zn/Zn^{++}}$ is that given by Clayton and Vosburgh, *viz.*, +0·7612 v. (American convention) at 25°, at which temperature the measurements were carried out.

The zinc-amalgam electrode was prepared by a modification of the method of Clayton and Vosburgh *loc. cit.*) and that of Tartar, Newschwander, and Ness (*ibid.*, 1941, **63**, 28). A stick of zinc of A.R. purity was dipped in a small pool of mercury beneath a concentrated solution of zinc sulphate slightly acidified with sulphuric acid and contained in a wide test-tube which was heated in a boiling water-bath for several hours. A considerable quantity of the zinc dissolved in the mercury but, at the same time, the stick became thoroughly amalgamated to a depth of 1 mm. or so. When not in use, the amalgamated zinc rod was kept under the zinc sulphate solution with its end in contact with the pool of amalgam. In this way the electrode was found to keep perfectly and to give entirely reproducible results.

The hydrogen electrode was of the Hildebrand type (*J. Amer. Chem. Soc.*, 1913, **35**, 847) and, like the zinc electrode, dipped directly into the $ZnCl_2$–HCl electrolyte which was contained in a bottle having a rubber stopper and an outlet for excess hydrogen. No liquid-junction potentials, therefore, had to be taken into account.

A series of measurements was made with $ZnCl_2$–HCl mixtures of total concentration 0·249N : the e.m.f. readings were steady and reproducible. Erratic and unsteady readings resulted with mixtures of lower concentration (0·1N, 0·05N), and the e.m.f. varied with the rate of flow of the hydrogen. It is known that dissolution occurs at a zinc electrode in dilute acid solutions, and evidently the flow of hydrogen affected this as a result of its stirring action. No evidence of dissolution was detected with the 0·249N-concentration.

Discussion.

An explanation of this proportionality of the activity coefficient ratios can be obtained from a consideration of the ionic atmospheres to which the cations in the resin phase are subjected. According to the Debye–Hückel theory, the activity coefficient of an ion is determined by the ionic atmosphere surrounding it. Now, the cations in the solid phase must be more or less fixed and hence can exert relatively little influence on one another. The ions in the aqueous phase, however, *can* approach close to those in the solid and can readily influence them. Thus a cation in the solid phase may be surrounded by an ionic atmosphere similar to that surrounding a corresponding cation in the aqueous phase, and its activity coefficient may, therefore, vary in a similar manner with the composition of the solution. The activity coefficients would be equal in the two phases only if the cation in the solid phase were completely surrounded by the aqueous ionic atmosphere.

Structure of the Multivalent Metal Salts of the Resin.—Since the sulphonate groups occupy irregular positions in the resin, it might be expected that, while a certain number of these would be in favourable position to be neutralised by the multiple valencies of multivalent ions, the rest would not be in such favourable positions and could not exchange their univalent for bivalent ions. In fact, the whole of the sulphonate groups can be as readily neutralised by multivalent ions as they are by univalent. (This was demonstrated by an experiment in which an excess of ammonium chloride solution was passed over a column of about 7 g. of washed H-resin, liberating 14·55 meq. of H^+. The resulting NH_4-resin was washed and similarly treated with an excess of thorium nitrate solution, liberating 14·60 meq. of NH_4^+, *i.e.*, virtually identical with the liberated H^+.)

This is best explained by supposing each multivalent, if not univalent, cation not to be associated closely with any particular sulphonate groups (two, three, or four, as the case may be), but to be distributed throughout the resin phase in positions of minimum potential energy. The ions will be held in stoicheiometric number by electrostatic forces.

This picture is in keeping with the concept of the resin phase being completely ionised though not dissociated—a structure similar to that of a crystal. Unlike the ions in the crystal, however, those in the resin will be situated in an irregular pattern, as the anions—the resin sulphonate groups—are also in irregular positions.

A similar phenomenon is encountered in the combination of dye anions with wool, where the maximum capacity of the wool for dye combination is found to be a constant whatever the valency of the dye anion (see Speakman and Elliot, *J. Soc. Dyers Col.*, Symposium, 1946; Astbury and Dawson, *ibid.*, 1938, **54**, 6; Gilbert, *Proc. Roy. Soc.*, 1944, **183**, *A*, 167).

The facile and complete exchange of the univalent cations in an organic exchanger by multivalent seems to be a property unique to this type of exchanger. It is found to occur also with a sulphonated-coal exchanger, a phenol-ω-sulphonate resin, and a resin based on sulphonated styrene and divinylbenzene. On the other hand, Patton and Ferguson (*Canadian J. Res.*, 1937, *B*, **15**, 103) showed that 80% only of the total Na^+ in their (inorganic) zeolite was readily exchangeable for Ca^{++}, while the remainder was very difficult to replace and, in fact, they succeeded in exchanging only 90% of the Na^+ even on prolonged contact with a very dilute calcium solution.

It is of interest that a synthetic resin similar to that used in the present study, but deliberately prepared with one-fifth of the number of sulphonate groups, showed a similar and even greater reluctance to exchange H^+ for Mg^{++}, although exchange for Na^+ occurred quite readily.

Patton and Ferguson found that, although their equilibrium results for a single concentration fitted the Rothmund–Kornfeld equation, the effect of dilution was less than would be expected from this equation, and they ascribed this to the uncertain and varying available (total) capacity.

In the light of this evidence it is probable that true equilibrium is rarely reached in " equilibrium " studies made with inorganic exchangers, and the results will depend considerably on time of contact and on dilution. This may well be the reason for the frequent contradictions between the results of different workers using similar materials.

Importance of Dissociation in Solution.—The affinity of the resin for the simpler univalent cations, whose salts are highly dissociated in aqueous solution, is readily obtained from the equilibrium constants, and the values obtained are independent of concentration, anion, etc. The influence of incomplete dissociation on the equilibrium position attained with thallous salts has been dealt with in Part I. It was shown that this, at present, makes it impossible to discover the primary factor determining the affinity of this ion for the resin.

FIG. 5.

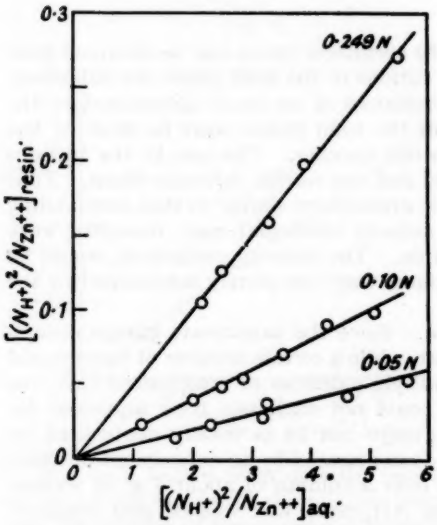
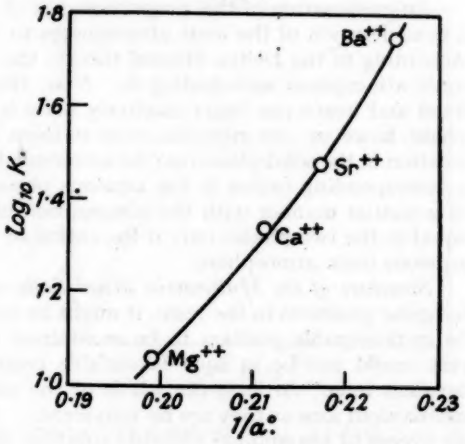


FIG. 6.



Incomplete dissociation is more commonly observed in the salts of multivalent cations, and it plays an important part in determining the extent of exchange with these ions. As with the thallous ion, the primary factor determining their affinities for the resin is largely hidden by this effect. An extreme case of incomplete ionisation is illustrated by the remarkably low affinity of the resin for the mercuric ion, which is taken up by a hydrogen resin and by an ammonium resin to an only just measurable extent from a 0·1 or 0·05N-solution of mercuric chloride (cf. table). The rôle of ionisation in determining the affinity of multivalent cations when associated with different anions in solution will be dealt with later.

The relation, if any, between affinity and ionic size should appear most clearly in the equilibria involving the alkaline-earth chlorides, which are typical strong electrolytes (Scatchard and Tefft, *J. Amer. Chem. Soc.*, 1930, **52**, 2281). Fig. 6 shows the graph of log K against $1/a°$ for this series. The values of $a°$, the distance of closest approach of the ions, are those of Stokes and Robinson (*ibid.*, 1948, **70**, 1870) and are, therefore, comparable with those used for the univalent cations (see Part I). The smooth curve so obtained might be an indication that ionic size does, in fact, play a determining rôle. This can be so if each bivalent ion in the resin phase is situated close to one of its neutralising sulphonate groups and relatively far from the other. Such a position might well be that of minimum potential energy. This arrangement may be reflected in the curvature of the graph as compared with the straight line obtained with the univalent ions, where only one sulphonate group per cation is involved and to which sulphonate group the cation evidently approaches closely.

All the salts of the ions Cd^{++}, Co^{++}, Ni^{++}, Zn^{++}, Mn^{++}, Cu^{++}, and Pb^{++} exhibit ion association

to such a marked extent (Scatchard and Tefft, *loc. cit.*) that this becomes a major factor determining the " affinity " of these ions. The measured affinity is the resultant of this secondary effect and the primary determining factor, which may or may not be ionic size, and it is exceedingly difficult to separate the two. This difficulty exists because activity coefficients reflect both degree of dissociation and ionic size (in terms of the a° parameter), and few data exist for the a° values and degrees of dissociation separately of the salts studied here. Knowledge of the latter can alone enable the true activities in the aqueous phase to be calculated and thus permit the primary factor to be studied.

Scatchard and Tefft (*loc. cit.*) calculated a° values for the chlorides of lead and zinc from the respective activity coefficients, taking into account the incomplete dissociation of the salts, and obtained the values 1·9 and 3·5—6, respectively. This, qualitatively, is in keeping with the higher affinity of the resin for lead than for zinc ions. No quantitative conclusions can be drawn, however, for the absence of figures for the respective degrees of dissociation precludes the calculation of the true activities in the aqueous phase.

Boyd, Schubert, and Adamson (*J. Amer. Chem. Soc.*, 1947, **69**, 2828) have suggested that the relative magnitude of a° for bivalent ions may be found directly from activity coefficient–concentration graphs and that, therefore, the " affinities " will be in the opposite order to the activity coefficients. This is, in fact, true only for the salts of the alkaline-earth ions, and it can scarcely apply to those ions whose salts exhibit ion association, since a low activity coefficient could be the result either of high ion association, leading to a low affinity, or of a small a° value, leading to a high affinity.

Using their theory, they predicted the affinities of the transition metals to be $Zn^{++} > Cu^{++} > Ni^{++} > Co^{++} > Fe^{++}$. In fact, the affinities of the first four of these lie in very nearly the reverse order (see Fig. 2 and table), *viz.*, $Co^{++} > Ni^{++} = Cu^{++} > Zn^{++}$.

Influence of the Anion on the Equilibrium Position.—In Part I the conflicting statements appearing in the literature on the influence of the anion have been discussed. It was shown that the dependence on the anion of the equilibria involving the thallous ion, and the corresponding independence of those involving the alkali-metal ions, is consistent with the assumption that the effect of the anion is to change the degree of dissociation of the salts in solution. Those anions which do not change the degree of dissociation of the two salts involved, or change it to the same extent, result in the same equilibrium; while those which cause an unequal change will result in a different equilibrium, the cation associated with the less dissociated salt showing a lesser tendency to pass into the resin phase.

The behaviour of equilibrium systems containing multivalent cations when the anion is changed, lends further support to this concept. As mentioned above, incomplete dissociation is more commonly observed in the salts of multivalent cations than in those of univalent, and this is reflected in a much greater dependence upon the anion of systems containing multivalent cations. In particular, less of the multivalent cation passes into the resin phase from solutions containing bivalent anions, *e.g.*, sulphate, than from solutions containing univalent anions. Thus, a uni–bivalent system of ammonium resin and magnesium salts showed the same equilibrium with the chloride and nitrate, but sulphate and formate caused less bivalent ion to pass into the solid phase. The NH_4^+–Mn^{++} system behaved in an identical manner. A system of bi–bi-valent ions, *viz.*, beryllium resin and magnesium salts, came to the same equilibrium position in the presence of the anions Cl′, NO_3', and SO_4''; the system Mg-resin–Mn^{++} behaved similarly. Systems involving tervalent ions were studied, *viz.*, NH_4-resin and Mg-resin, respectively, with the chloride and sulphate of aluminium. Less of the higher-valent cation passed into the solid phase in the presence of SO_4'' than in the presence of Cl′.

Ter- and Quadri-valent Cations.—Because the exchange lies so far to one side, and the third and fourth powers of concentration appear in the mass-action expression, it is difficult to test the law of mass action for these ions. However, assuming its validity, approximate values of the stoicheiometric equilibrium constants are 4·1 for Al^{+++} (sulphate solution) and 0·6 for Th^{++++} (nitrate solution), where

$$K_{Al} = [(C_{NH_4^+})^3/C_{Al^{+++}}]_{aq.}[N_{Al^{+++}}/(N_{NH_4^+})^3]_{resin} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

and

$$K_{Th} = [(C_{NH_4^+})^4/C_{Th^{++++}}]_{aq.}[N_{Th^{++++}}/(N_{NH_4^+})^4]_{resin} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

[The N terms are as defined in equation (5), and the C terms are expressed in equivs. per litre.]

Both these values, and particlarly that for Th^{++++}, represent a very strong binding of the ion by the resin, as Fig. 1 (inset) shows. In agreement with earlier work, the affinity of the ions is seen to increase with increasing charge.

The general influence of charge has been tacitly assumed, in the past, to be in accordance with Coulomb's law. This is correct only if the multivalent cation is situated close to one of its neutralising sulphonate groups (presumably at the $a°$ distance) and relatively far from the others. The interaction energy between the cation and its nearest sulphonate group is then

$$E = ze^2/Da° \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

(z = valency of cation and D = dielectric constant), while an additional contribution is provided by the attraction of the more distant sulphonate groups. The total interaction is, therefore, greater than z times $e^2/Da°$, which is that of z univalent ions of the same size. A comparison of the $a°$ values given in the literature indicates that uni- and bi-valent ions, at least, are very nearly the same size.

If the multivalent cation were situated more or less at the "centre of gravity" of the z negative groups, the interaction energy would be considerably *less* than that of z univalent cations, each situated close to a sulphonate group. This model is consistent with that derived above from other considerations.

In spite of its quadruple charge, the zirconium ion goes on to the resin from a solution of its nitrate to only a very small extent, its equilibrium constant against NH_4^+ being *ca.* 4×10^{-6} (cf. the value for thorium and Fig. 1 inset). This, without doubt, is due to the very small number of free Zr^{++++} ions present in solution, in consequence of the tendency of zirconium to form complex anions (see Hopkins, "Chapters in the Chemistry of the Less Familiar Elements," Stipes Publishing Co., 1939, Chap. 12, pp. 7 *et seq.*).

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261. *Cation Exchange with a Synthetic Phenolsulphonate Resin. Part III. Equilibria with Large Organic Cations.*

By T. R. E. KRESSMAN and J. A. KITCHENER.

The affinity of some large organic cations, *viz.*, quaternary ammonium salts and the quininium ion, for a phenolsulphonate resin increases with increasing size of the ion. This is in contrast to the simple inorganic cations and suggests that van der Waals forces contribute largely to the affinity, the Coulomb forces being less important. This is supported by the greater affinity for the resin of the trimethyl-*n*-amylammonium ion than of the isomeric tetraethylammonium ion. The rates of exchange, on the other hand, decrease with increasing ionic size.

The saturation capacity is the same for the largest of the quaternary ions studied, *viz.*, phenylbenzyldimethylammonium, as for inorganic ions, indicating that all the molecular pores within the resin are larger than the effective diameter of this ion. The quininium ion, however, appears to be larger than some, at least, of the pores, as it exhibits an apparently lower affinity than its size would suggest.

No physical adsorption is observed from solutions of highly dissociated salts of large cations.

THE exchange of organic cations from aqueous solutions of their hydrochlorides with a calcium zeolite was studied by Ungerer (*Kolloid-Z.*, 1925, **36**, 228). However, his results were complicated by a simultaneous exchange of hydrogen ion, produced from the hydrolysis of the salts and, accordingly, seem inconclusive. This factor was eliminated in the present work by using neutral salts only of the organic cations.

EXPERIMENTAL.

The present study was carried out at 25° with the same phenolsulphonate resin (−10 + 20 mesh) and the same technique as used in Parts I and II (preceding papers). Quaternary ammonium salts were used, as they have the advantage of being readily prepared in a pure state and the quaternary ion can be built up and modified at will. In addition, with the exception of the tetramethylammonium and possibly tetraethylammonium ion, they are completely unhydrated in solution (J. O'M. Bockris, private communication), and the ionic size can be calculated with fair accuracy from the known C–C, C–N, and C–H bond lengths.

The parent ammonium ion was used as the reference ion in the resin, which was allowed to come to equilibrium with the quaternary bromide in every case, for, although it has been shown in Part I that equilibria among univalent inorganic cations are largely independent of the anion, it was considered more satisfactory to maintain the same anion with these hitherto unstudied ions.

It was found that, as the ion was made larger, the rate of attainment of equilibrium became less and, accordingly, it was necessary to allow prolonged periods for equilibrium to become established.

True equilibrium was considered to have been attained when two identical experiments showed the same amount of exchange when allowed to remain for different periods of time.

The tetramethylammonium ion in 0·1N-solution reached equilibrium in a matter of hours, although about 5 days were, in fact, allowed; on the other hand, the phenylbenzyldimethylammonium ion required a minimum of 6 weeks. When the study was extended to quinine hydrochloride, a 0·05N-solution had not reached equilibrium even after 20 weeks (see Fig. 2).

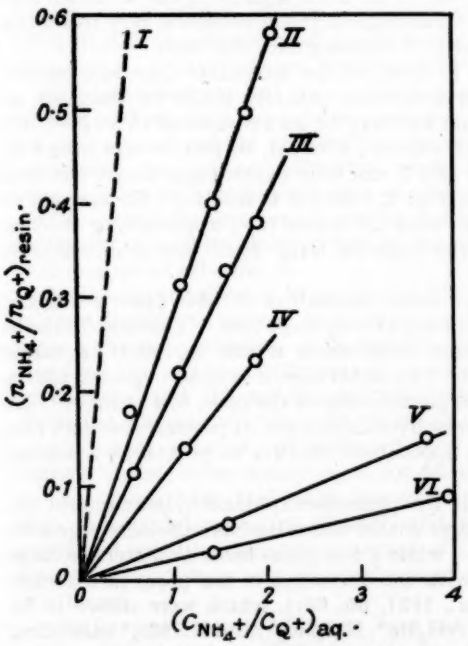
Results and Discussion.

The equilibria attained are plotted in Fig. 1 in terms of the mass-action functions, and the equilibrium constants, obtained from this graph, are given in the table. The equilibrium constant is defined by

$$K = [C_{NH_4^+}/C_{Q^+}]_{aq.}/[n_{NH_4^+}/n_{Q^+}]_{resin} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

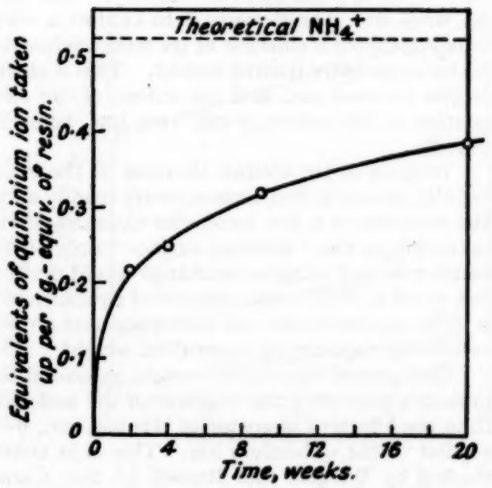
where the n terms are the numbers of the specified ions in the resin phase at equilibrium, and the C terms are the corresponding aqueous concentrations.

Fig. 1.



I, NH_4^+. IV, $(NMe_2Am^n)^+$.
II, NMe_4^+. V, $(NMe_2EtPh)^+$.
III, NEt_4^+. VI, $(NMe_2Ph{\cdot}CH_2Ph)^+$.

Fig. 2.



These figures show that the affinities (as measured by the equilibrium constant) *increase* with increasing ionic size. This clearly indicates that the ion is held on the resin by a different set of forces from those binding simple inorganic ions, where the affinity decreases with increasing size, and suggests that van der Waals forces are contributing very considerably to the affinity (cf. also Hendricks, *J. Physical Chem.*, 1941, **45**, 65). The Coulomb forces, which are predominant in determining the affinity of the inorganic cations, are here playing a minor rôle. In this respect the behaviour of the large ions towards the resin is similar to that of dye ions towards a textile fibre.

It is not readily possible to calculate van der Waals contributions quantitatively; nevertheless, it is clear qualitatively that the interaction between the large ion and the surface on which it is bound should increase with the number of atoms in the ion which are able to come within a few Ångstrøm units of the surface. In agreement with this view, the trimethyl-*n*-amylammonium ion is seen (Fig. 1 and table) to have a higher affinity than the isomeric tetraethylammonium ion: models show that the former can be arranged with a larger number of atoms within a few A. of a surface than the latter.

TABLE I.

Ion.	Equilm. const.	No. atoms in contact with surface (not counting hydrogen).	Major diam. A.
Ammonium	1·00	0	2·4 *
Tetramethylammonium	3·67	3	4·6
Tetraethylammonium	5·0	6	7·2
Trimethyl-*n*-amylammonium	8·24	7	9·5
Phenyldimethylethylammonium	25·2	9	8·5
Phenylbenzyldimethylammonium	44·4	14	11·2

* Hydrated size, calculated from mobility (73·7) by the formula given by Walden (" Elektrochemie nichtwassriger Losungen," 1924 edn., p. 189). The sizes of the (unhydrated) quaternary ions are calculated from models, using the bond lengths given by Pauling (" The Nature of the Chemical Bond," 1944 edn., pp. 160 *et seq.*).

All the quaternary ions so far studied are of a size less than that of the smallest molecular channel within the resin, since the saturation capacity (or equivalent weight) is the same for the largest of them, *viz.*, phenylbenzyldimethylammonium, as for the simple inorganic ions (see also Part I). As already mentioned, however, the *rate* of exchange of the large ions is very much less in spite of the higher affinity, because of the difficulty of diffusing into the resin.

Presumably, if the ion were larger than some, at least, of the molecular channels, certain parts of the resin would be inaccessible and a lower saturation capacity would be observed, as well as an apparently lower affinity. The quininium ion may be an example of this effect, for its large size should cause it to exhibit a very high affinity, whereas, in fact, it was found to exchange from a solution of its monohydrochloride (pH 7) not only exceedingly slowly but also to an apparently limited extent. This is clear from Fig. 2, where it is seen that the rate curve begins to level out, and the extent of the exchange after 20 weeks (*i.e.*, approaching the flat portion of the curve) is still very low, being less even than for NH_4^+ itself (see broken line in Fig. 2).

In spite of the overall slowness of the exchange, about one-half of it takes place relatively rapidly, showing that some sites are readily accessible even to very large ions. This may indicate the presence of a few molecular channels of very large diameter, or it may represent exchange occurring on the " external surface " only of the resin. In either case it is to be expected that a faster rate and a higher exchange would occur as the particle size of the resin was reduced. As described in Part I, the position of equilibrium is normally independent of particle size, and this is to be expected where all the sulphonate groups are accessible to the ion, as proved by a normal saturation capacity or equivalent weight.

The normal equivalent weight exhibited towards the phenylbenzyldimethylammonium ion indicates that even the smallest of the molecular pores within the resin have diameters greater than the effective diameter of this ion, *viz.*, 6—11 A., while a few pores have diameters as large as that of the quininium ion. This is in contrast with the diameters of the pores in a zeolite studied by Wiegner and Russell (*J. Soc. Chem. Ind.*, 1931, **50**, 65T), which were shown to lie between 3 and 5 A., even such relatively small ions as NH_3Me^+, $NH_2Me_2^+$, and $NHMe_3^+$ exhibiting a progressively reduced affinity for the zeolite. The pores are also larger than those in a polyhydric phenolic resin studied by Akeroyd and Broughton (*J. Physical Chem.*, 1938, **42**, 343), many of which were less than about 9 A., in diameter, as indicated by the considerably reduced affinity for the benzyltrimethylammonium ion.

No physical adsorption of the salts or organic cations occurs, even when the cation is as large as phenylbenzyldimethylammonium, presumably because of the nearly complete dissociation of these salts.

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262. *Cation Exchange with a Synthetic Phenolsulphonate Resin. Part IV. A Note on Equilibria in Presence of Non-aqueous Solvents.*

By T. R. E. Kressman and J. A. Kitchener.

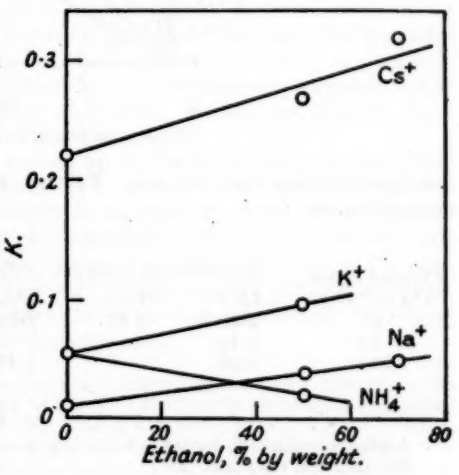
Cation exchange occurs readily between a phenol-sulphonate resin and cations in mixtures of water and non-aqueous solvents. The equilibria are found to obey the law of mass action, concentrations being used. More potassium ion passes into the solid phase in the NH_4^+–K^+ system in aqueous ethanol and aqueous acetone than in pure water. In aqueous ethanol the logarithm of the equilibrium constant is a linear function of the alcohol concentration; in aqueous acetone the equilibrium constant itself varies linearly with the acetone concentration. This behaviour cannot be explained by differences of hydrated cationic size: however, an explanation may lie in the influence of solvent on the a° values. The effect of incomplete dissociation on the equilibrium constant is very marked with manganous sulphate in aqueous ethanol.

Very few studies have been made of equilibria between cation exchangers and solutions of salts in the presence of non-aqueous solvents. Only a single set of data appears in the literature (Wiegner and Muller, *Z. Pflanz. Dung.*, 1929, **14**, *A*, 332; Wiegner and Jenny, *Kolloid-Z.*, 1927, **42**, 270) in which the solvent was aqueous alcohol and the exchanger a synthetic aluminosilicate. No study has been reported with a resinous exchanger.

The present study has been limited to aqueous ethanol and aqueous acetone as solvents at 25°, but it is clear from the results that the subject is a complex one and considerably more work is necessary before any general rules can be formulated. Certain limitations are set by the extreme scantiness of activity data of salts in the presence of non-aqueous solvents.

In the experiments of Wiegner *et al.* (*locc. cit.*) a calcium zeolite was allowed to come to equilibrium with sodium, potassium, and cæsium chlorides dissolved in aqueous ethanol of various concentrations, and the results indicated that more alkali ion passed into the solid phase as the concentration of ethanol was increased, and the exchange became more nearly equal for all the ions. It was shown that the exchange varied linearly with the concentration of ethanol, and this was correlated with the dielectric constant of the mixture, which similarly varies with the concentration of ethanol.

Fig. 1.



Similar experiments have now been carried out with a calcium resin (prepared from the same resin as that used in Parts I—III) and 0·05N-solutions of sodium, potassium, and cæsium chlorides. The results, illustrated in Fig. 1, show that more alkali ion likewise passed into the solid phase with increasing alcohol content of the solvent, in agreement with the findings of Wiegner *et al.* The extent of exchange, however, showed no tendency to become equal for the several ions. The ammonium ion behaved conversely to the alkali ions and showed a reduced affinity as the proportion of ethanol was increased.

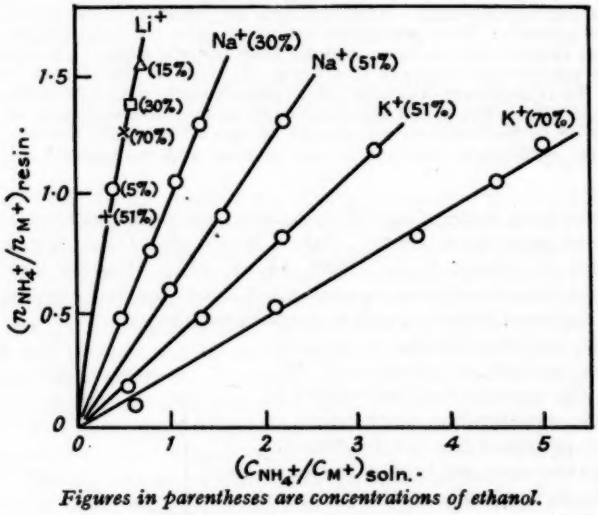
This suggests that, in exchanges between ammonium and the alkali-metal ions, the resin would show an increased affinity for the latter by comparison with the former as the ethanol concentration is increased and this, in fact, is found to be the case. Table I shows the values of the stoicheiometric equilibrium constants obtained for some alkali-metal ions in 0·1N-chloride solution and the resin initially in the ammonium form. The equilibrium constant is defined by

$$K = (n_{M^+}/n_{NH_4^+})_{resin}(C_{NH_4^+}/C_{M^+})_{soln.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and was obtained from the slopes of the straight lines which result on plotting $(n_{NH_4^+}/n_{M^+})_{resin}$ against $(C_{NH_4^+}/C_{M^+})_{soln.}$ (see Fig. 2). (The n terms in these expressions are the number of equivalents of the specified ion in the resin at equilibrium, and the C terms are the corresponding solution concentrations.) A linear relationship exists between the logarithm of the equilibrium constant and the ethanol concentration, although the equilibrium constant of the Li^+–NH_4^+ system remains the same as in pure water, even up to 70% alcohol.

The K^+–NH_4^+ equilibrium (NH_4-resin and KCl) has been studied in aqueous acetone solution also. Straight lines were also obtained on plotting the appropriate mass-action functions (equation 1), and the equilibrium constants obtained from these are given in Table II. The change of equilibrium constant with acetone concentration, although in the same direction, is

FIG. 2.



Figures in parentheses are concentrations of ethanol.

less marked than with ethanol. Further, the equilibrium constant varies linearly with acetone concentration.

TABLE I.

Ethanol concn. (% by wt.).	Equilibrium constant (25°). LiCl.	NaCl.	KCl.	Ethanol concn. (% by wt.).	Equilibrium constant (25°). LiCl.	NaCl.	KCl.
0	0·40	0·67	1·05	30·5	0·40	1·04	2·04
5·0	0·40	—	—	51·5	0·40	1·67	2·73
15·5	0·40	—	1·47	70·5	0·40	—	4·25

TABLE II.

Acetone concn. (% by wt.)	0	31·0	50·9	71·0
Equilibrium constant (25°)	1·03	1·64	1·97	2·28

TABLE III.

Salt and normality.	Equilm. const. in 51·5% EtOH.	Equilm. const. in H_2O.	Salt and normality.	Equilm. const. in 51·5% EtOH.	Equilm. const. in H_2O.
$BaCl_2$, 0·1	23·0	5·64	$MnSO_4$, 0·1	0·036	0·82
$MnCl_2$, 0·1	1·14	1·00	,, 0·05	0·44	0·82

Table III shows the equilibrium constants at 25° for an ammonium resin and solutions of barium chloride, manganous chloride, and manganous sulphate in 51·5% (by weight) aqueous ethanol. These are defined by

$$[(C_{NH_4^+})^2/C_{M^{++}}]_{soln.} = K[(N_{NH_4^+})^2/(N_{M^{++}})]_{resin} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and are obtained from the slopes of the straight lines which result on plotting the appropriate mass-action functions. (Each N term in this equation is the ratio of the number of equivalents of the cation to the total number of equivalents of the two cations in the resin phase; the C terms are the concentrations of the ions in the solution phase, in equivs per l.) A comparison of the figures with those obtained in pure water shows that barium ion in 0·1N-chloride solution has a higher affinity for the resin in 51·5% aqueous ethanol than in pure water, while manganese ion in 0·1N-chloride shows almost the same affinity as in water. On the other hand, the latter ion in 0·1N-sulphate solution shows a very much lower affinity in the aqueous-alcoholic solution than it does in water—comparable, in fact, with that of lithium. In 0·05N-solution the affinity

is greater, by comparison with that in 0·1N-solution, than is predicted by the mass-action equation (2), as indicated by the different K.

Discussion.—The results expressed in Table I could perhaps be explained on an assumption, similar to that of Wiegner *et al.* (*locc. cit.*), that the alkali-metal ions are dehydrated by the alcohol to a greater extent than is the ammonium ion. This theory seems to be untenable, however, as measurements of the mobilities of the potassium and the ammonium ions, carried out in aqueous-ethanolic solution containing 51·5% by weight of alcohol, showed these to be very nearly equal, *viz.*, 50·1 and 51·5, respectively, just as they are in pure water. Consequently, the hydrated radii must be practically equal. It is possible, however, that the $a°$ values of the two ions have changed to different extents in the alcoholic solution, and since the equilibria are determined by these values rather than by hydrated radii, this would account for the observed effect. Unfortunately, no data exist from which these values can be calculated and it is, accordingly, impossible to test this theory.

Certainly the different behaviour of the lithium ion precludes any correlation with dielectric constant as attempted by Wiegner (*loc. cit.*), since this would presuppose a similar variation with alcohol concentration in each case.

Similar considerations evidently apply to the NH_4^+–Ba^{++} equilibrium. The behaviour of the manganous ion in sulphate solution, however, indicates that here the "affinity" is largely determined by the degree of dissociation of the manganous sulphate. The low value of the equilibrium constant in 0·1N-alcoholic solution is evidently the result of the very slight ionisation of the manganous sulphate, few manganese ions being available to pass into the resin phase. Dilution increases the ionisation and more of these ions therefore pass into the solid phase than is predicted by equation (2), and a different equilibrium "constant" is obtained in 0·05N-solution. An indication of the very small dissociation of manganous sulphate is the difficulty with which it dissolves in the aqueous alcohol solution. Manganous chloride, and especially barium chloride, on the other hand, dissolve readily.

It is interesting to speculate upon the state of ionisation of the metal salts of the resin. Whereas the degree of dissociation of an aqueous electrolyte changes with the addition of a non-aqueous solvent, that of the resin salt must apparently be supposed the same in the presence of all solvents. According to present theory, incomplete dissociation of a salt in solution is not generally due to the existence of covalent linkages, but to the presence of ion pairs, triple ions, etc. (see, *e.g.*, Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," 1943, pp. 183 *et seq.*). Presumably a similar situation exists in the resin salts, which may, therefore, be regarded as completely ionised but almost entirely undissociated.

We are indebted to Professor H. V. A. Briscoe for his continued encouragement and interest in the work described in this and the preceding three papers, and to Dr. J. O'M. Bockris for helpful discussion on the theory of electrolytic solutions. One of us (T. R. E. K.) thanks The Permutit Co., Ltd., Chiswick, W.4, for a grant in support of the work and for permission to publish these four communications.

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263. *The Oxidation of Aldoses by Hypoiodous Acid. Part II.*

By O. G. INGLES and G. C. ISRAEL.

It was recently shown that the active oxidising agent in the reaction between aldoses and alkaline solutions of iodine is hypoiodous acid. This reaction has now been further investigated, and the complete mechanism in alkaline solution is shown to be the oxidation of aldopyranose by hypoiodous acid to aldonic acid. The reaction is shown to be of second order. It is shown that glucono-δ-lactone is produced as an intermediate when the reaction is carried out below pH 7, but this is not necessarily the case in alkaline solution.

Some further steric effects on the rate of oxidation are reported and discussed.

WE have shown (*J.*, 1948, 810) that when a number of aldopentoses and aldohexoses are oxidised by alkaline solutions of iodine, the active oxidising agent is un-ionised hypoiodous acid. In the course of the oxidation of aldoses by hypoiodous acid, two reactions occur simultaneously, viz.,

$$3HIO \longrightarrow IO_3^- + 2I^- + 3H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

$$C_6H_{12}O_6 + HIO \longrightarrow C_6H_{12}O_7 + I^- + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)$$

Reaction (A) has been investigated by several workers who have shown that it is of second order (Schwicker, *Chem.-Ztg.*, 1891, **15**, 630; Giuseppe d'Este, *Boll. Chim. Farm.*, 1939, **78**, 117; Skrabal, *Monatsh.*, 1907, **28**, 319; 1909, **30**, 51; *Chem.-Ztg.*, 1905, **29**, 550). We have investigated the order of reaction (B) by determining the relative rates of oxidation of glucose at two different initial concentrations, account being taken of the simultaneous formation of iodate. Starting with equal concentrations (a) of glucose and of hypoiodous acid in the reaction mixture, the time (t) for a given fraction of the oxidation to occur was determined. The apparent order of the reaction was then calculated from the formula $n = 1 + (\log t_1/t_2)/\log (a_2/a_1)$, where t_1 and t_2 are the times for a given fraction of the reaction to occur for initial concentrations a_1 and a_2, respectively. The results are summarised in Table I.

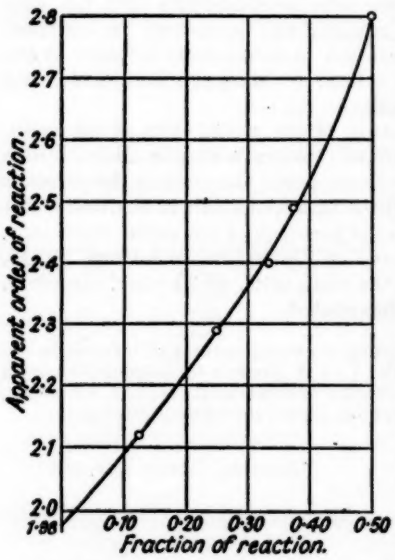
TABLE I.

Times of fractional change and apparent order of reaction.

Initial concns.: $a_1 = 0{\cdot}1667$M; $a_2 = 0{\cdot}1000$M. pH = 11·15.

Fraction of reaction (x)	0·125	0·250	0·333	0·375	0·500
t_1 (secs.)	2·6	5·0	6·7	7·9	14·0
t_2 (secs.)	4·6	9·7	13·8	17·0	35·0
n	2·12	2·29	2·40	2·49	2·80

The marked drift in the values of n so obtained is due to the fact that the formula given above is not strictly applicable. This formula applies in the case where both reactants are at equal concentrations at each stage during the reaction. However, in this particular case, the simultaneous formation of iodic acid by reaction (A) results in the concentration of hypoiodous acid becoming progressively lower than that of glucose at any given time during the reaction. To eliminate this factor values of n were plotted against values of x (see fig.), and the plot extrapolated to $x = 0$, which gives the value of n as 1·98. Hence it is clear that the reaction is of second order within the limits of experimental error.



The product of the oxidation of glucose in alkaline solution has been investigated by an ion-exchange method, and shown to be gluconic acid. The possibility that oxidation proceeds further than this stage to give saccharic acid has been eliminated, and it has been found that no degradation of the glucose molecule occurs. Experiments made on the rate of oxidation of both mannitol and gluconic acid under similar conditions to those employed in the oxidation of aldoses have been performed and in neither case was oxidation observed. Thus it is clear that hypoiodous acid does not attack either primary or secondary alcohol groups in a normal aldopyranose.

Since Isbell (*J. Res. Nat. Bur. Stand.*, 1932, R.P. 441; 1933, R.P. 534) has shown that the oxidation of glucose by bromine at pH 6·4 leads directly to glucono-δ-lactone, it is possible that oxidation by hypoiodous acid proceeds through a similar intermediate. We have found that the oxidation of glucose by hypoiodous acid at the same pH (6·4) follows a similar course. However, it does not necessarily follow that when the oxidation is carried out in alkaline solution, this same mechanism is operative, and attempts to detect any intermediate lactone at the normal pH of oxidation, *i.e.*, pH 11·35, have so far been unsuccessful. At such a pH, any lactone formed would be immediately saponified.

In our previous paper (*loc. cit.*) some effects of configuration of the carbohydrate chain in several aldohexoses and aldopentoses on the rate of oxidation by hypoiodous acid were reported. Experiments on the oxidation of further aldose derivatives, namely L-rhamnose, 2 : 3 : 4 : 6-tetramethyl glucose, α-methylglucoside, lactose, cellobiose, and melibiose have provided further information on these effects. Rhamnose is oxidised at the same rate as mannose; 2 : 3 : 4 : 6-tetramethyl glucose is oxidised at almost the same rate as glucose; α-methylglucoside is not attacked, and the disaccharides of aldopyranoside–glucose type are oxidised at a rate distinct from that of any monosaccharide, and more slowly than glucose. The active oxidising agent

in all cases was shown to be hypoiodous acid. The relative rates of oxidation are shown in Table II, those found by Myrbäck (see Ingles and Israel, *loc. cit.*) being added for comparison.

TABLE II.

Sugar.	Relative rate.	Relative rate (Myrbäck).	Sugar.	Relative rate.	Relative rate (Myrbäck).
D-Glucose.....	1·00	1·00	Cellobiose	0·82	0·76
2 : 3 : 4 : 6-Tetramethyl glucose	0·95	0·68	Lactose	0·81	0·76
			Melibiose.....	0·78	0·78
D-Mannose	0·24	0·24	Maltose	—	0·79
L-Rhamnose	0·26	0·20			

(α-Methylglucoside is not attacked.)

It is apparent from these and from our previous results that: (i) Similar configurations on carbon atoms 2, 3, and 4 give rise to the same rate of oxidation. (ii) Replacement of $CH_2 \cdot OH$ in an aldose by H or by CH_3 has little or no influence on the rate of oxidation. (iii) Methylation of the hydroxyl groups on carbon atoms 2, 3, 4, and 6 of glucose has only slight effect on the rate of oxidation of this sugar (this conflicts with Myrbäck's finding). (iv) The presence of an aldopyranoside linkage depresses the rate of oxidation of glucose, but this rate remains independent of the nature of the aldopyranoside present. (v) Methylation on carbon atom 1 protects an aldose from attack by hypoiodous acid. This finding is in agreement with (iv) above, that pyranosidic groups are not attacked.

EXPERIMENTAL.

Materials.—All sugars used were checked for purity by measurement of their specific rotations, the values found being as follows: L-rhamnose (hydrate), $[\alpha]_D^{20°}$ + 8·13° (Bates, "Polarimetry and Saccharimetry of the Sugars," U. S. Dept. of Commerce, 1942, + 8·20°); 2 : 3 : 4 : 6-tetramethyl glucose, $[\alpha]_D^{20°}$ + 83·4° (Bates, + 83·3°); lactose (hydrate), $[\alpha]_D^{20°}$ + 52·5° (Bates, + 52·6°); cellobiose, $[\alpha]_D^{20°}$ + 33·8° (Bates, + 34·6°); melibiose, $[\alpha]_D^{20°}$ + 129·0° (Bates, + 129·5°); α-methylglucoside, $[\alpha]_D^{20°}$ + 157·5°, m. p. 166° (Bates, + 158·0°, m. p. 166°). All other materials used were B.D.H. "AnalaR" reagents.

Kinetic Methods and Buffer Solutions.—These have been described in our previous paper (*loc. cit.*).

Determination of the Order of Reaction.—The experimental technique was similar to that previously employed, the initial concentration of iodine, however, being equimolecular with that of glucose.

Direct acidification of a reaction mixture liberates iodine proportional to iodate and hypoiodite, and titration with sodium thiosulphate then gives the sum of these, together with free iodine and tri-iodide (T).

The amount of hypoiodous acid removed by reaction with glucose at any instant is thus given by $T_0 - T_t$, where T_0 is the titre at zero time, and this value is also proportional to the amount of glucose oxidised at any instant. Experimental results are given in Table III. Plotting of these data enables

TABLE III.

Amount of glucose oxidised ($T_0 - T_t$) (titres against 0·01N-$Na_2S_2O_3$).

	Time (secs.).										
Concn. ...	0	3	4	5	7	9	10	15	20	25	30
M/10	0·00	2·20	3·00	3·54	—	6·16	6·74	9·20	10·50	—	12·44
M/6	0·00	4·00	—	—	9·60	—	12·20	14·25	15·05	16·80	17·25

times of fractional change to be read, and these have been shown in Table I. Hence, as shown in the discussion, the order of reaction was determined.

Determination of Gluconic Acid.—A solution of glucose in 0·1M-sodium carbonate was treated with an amount of solution of iodine in potassium iodide in excess of that theoretically required for the complete oxidation of the glucose, and the reaction was allowed to proceed to completion. The resultant solution was then passed through a column containing a cation exchange resin (Zeo-Karb 215) whereby the cations other than hydrogen ion were removed, and subsequently through a column containing an anion exchange resin (De-Acidite B). In the latter column, iodide ions were adsorbed preferentially to the anions of any organic acids present or to carbonate ion. The resultant dilute solution had a pH in the region 5·3—5·6. This solution was then evaporated to small volume (whereby any carbonic acid present was removed), and was then treated with a large excess of absolute alcohol, whereupon a semi-colloidal suspension separated. This suspension was separated by centrifuging and was shown to be gluconic acid by the method of Bennet-Clark (*Biochem. J.*, 1934, **28**, 45).

Following this method a 9·0 mg. sample of the alcohol-insoluble extract from the ion-exchange columns was dissolved in 8 ml. of water; 5 ml. of saturated ammonium molybdate and 2 ml. of glacial acetic acid were added, and the mixture allowed to stand for 3 hours in the dark, the rotation being then measured. The amount of gluconic acid in the sample was found to be 8·7 ± 0·1 mg. The alcohol extract was examined for organic materials with negative results.

By submitting a 280 mg. sample of glucose to oxidation by excess of hypoiodous acid, and examining the solution from the anion exchange column for gluconic acid by the same method, 273 mg. of gluconic acid were found, *i.e.*, 90% of theory.

Investigation for Possible Intermediates.—All attempts to identify an intermediate lactone when oxidation is carried out at high pH proved negative. However, working in the range of maximum lactone stability, *i.e.*, slightly on the acid side of the neutral point, an intermediate δ-lactone was detected. A comparatively concentrated solution (~ 0·15N) of hypoiodous acid was prepared by a slight modification of Koene's method (*Pogg. Ann.*, 1844, **56**, 302): 0·4 g. iodine was dissolved in 50 ml. of 95% alcohol, and the solution was shaken for 45 secs. with 0·8 g. of mercuric oxide to remove the hydriodic acid formed. The solution was rapidly filtered (30 secs.) through a layer of mercuric oxide supported on asbestos. The alcoholic solution of hypoiodous acid so obtained was straw-yellow in colour, and was used immediately to forestall major decomposition. 5 Ml. of this solution were added to 25 ml. of glucose solution containing 0·1125 g. of glucose, buffered to a pH of 6·4 by means of a suspension of barium carbonate, through which carbon dioxide was bubbled. After 10 minutes, any excess of iodine was removed by shaking with phellandrene, which simultaneously floats off the barium carbonate (Polya and Ingles, *J. Proc. Aust. Chem. Inst.*, 1947, **14**, 519). The solution was again shaken with mercuric oxide to remove any traces of hydriodic acid or iodic acid still present, and filtered. The pH of the resultant solution was followed over a period of time by means of a Coleman pH-meter, and was observed to fall progressively from approximately 6·1, immediately after the reaction had been stopped, to a constant valve of 2·8, some 2 hours later. This must indicate δ-lactone formation, and its subsequent transformation into gluconic acid (Isbell, *loc. cit.*, 1933). May, Weisberg, and Herrick (*J. Wash. Acad. Sci.*, 1929, **19**, 443) have found the acid dissociation constant of gluconic acid to be $1{\cdot}65 \times 10^{-4}$. On this basis, the pH of a solution containing 0·1225 g. of gluconic acid in 30 ml. (the theoretical amount obtained from 0·1125 g. of glucose) would be 2·70, in good agreement with the value observed.

Other Oxidation Experiments.—Mannitol, gluconic acid, and α-methylglucoside, submitted to the usual oxidation procedure, showed no change of titre after 15 minutes of reaction time, except in the case of α-methylglucoside at very high pH. This was probably due to slight hydrolysis. The results are shown:

α-Methylglucoside (titres against 0·02N-$Na_2S_2O_3$).

	pH. 11·20				pH. 12·80			
Time (mins.).	0	1	3	10	0	1	3	10
Titre.	13·20	13·18	13·18	13·18	13·20	13·05	12·95	12·75

Further confirmation that un-ionised hypoiodous acid is the active oxidising agent when aldoses are oxidised by alkaline solutions of iodine has been obtained by measurement of the oxidation rate of glucose in buffer solutions containing veronal of lower pH than those previously used. The theoretical values for the time of quarter change have been obtained from the theoretical curve of concentrations of un-ionised hypoiodous acid given in our previous paper (*loc. cit.*). The results are as follows:

Time of quarter change (secs.).

pH.	Calc.	Obs.	pH.	Calc.	Obs.
9·60	55	53	9·45	88	85

In addition, three disaccharides, 2 : 3 : 4 : 6-tetramethylglucose, and rhamnose were submitted to oxidation by hypoiodous acid. Experimental results are shown below:

Times of quarter change (seconds).

pH.	Lactose.	Melibiose.	Cellobiose.	Rhamnose.	2 : 3 : 4 : 6-Tetramethyl glucose.
9·60	—	—	60	—	—
10·60	7¾	8¼	6¾	—	6½
10·95	—	—	5	17	4¼
11·35	—	—	—	12½	3½
11·60	—	—	4½	—	—
11·80	—	—	—	—	4½
11·90	7½	8¼	6¾	—	—
12·00	—	—	—	25	6
12·80	45	47	48½	147	41

From these results the relative rates of oxidation of these sugars, compared with glucose as 1·00, can be readily calculated as in our previous paper.

The authors wish to express their indebtedness to Professor Schlubach, Hamburg, for the supply of samples of cellobiose and melibiose, and the Permutit Company, Sydney, for the supply of the ion-exchange resins used in this investigation.

UNIVERSITY OF TASMANIA, HOBART. [*Received, October 18th*, 1948.]

264. *The Comparison of Weak Neutron Fluxes by using Ethyl Iodide.*

By P. F. D. Shaw and C. H. Collie.

A quantitative study of the factors influencing the reproducibility of extractions of radioactive iodine from neutron-irradiated ethyl iodide has been made with a view to furnish a sensitive method of comparing weak neutron fluxes. Exchange rates between the radioactive species produced and the inactive ethyl iodide have been measured, and their bearing on the reproducibility is discussed. This method being used, the statistical error of the counts obtained from a weak neutron source was reduced from 14% for dysprosium oxide and indium detectors to 1%.

In comparing neutron fluxes it is desirable that the number of counts derived from them should be large and the statistical error small. To obtain a larger count use has been made of the fact that after ethyl iodide has been irradiated with neutrons a proportion of the radioactive iodine atoms produced can be extracted chemically together with a trace of carrier (Szilard and Chalmers, *Nature*, **1934**, **134**, 462). This is because the recoil energies of the iodine atoms from the γ-rays emitted upon capture of the neutrons are greater than the chemical binding energies of the C–I bonds, and consequently the ethyl iodide dissociates, leaving some of the radioactive iodine combined in some new chemical species (Glückauf and Fay, *J.*, 1936, 390), some of which can be extracted conveniently by means of an aqueous solution. In this way the radioactive iodine atoms produced throughout a large volume of ethyl iodide can be concentrated under a β-ray counter as silver iodide, so that self absorption of the β-particles is negligible.

This paper presents a quantitative study of some of the factors influencing the reproducibility of such extractions in the case of ethyl iodide. Initially the reproducibility was less than $\pm 5\%$, but by following the corrections and technique suggested in the following sections the experimental error can be reduced to about $\pm 0{\cdot}5\%$.

Experimental.

For the purpose of testing the reproducibility of the extractions, the irradiations and extractions of the ethyl iodide were performed in a basement, the temperature of which was nearly constant, and where the diffuseness of the light greatly reduced the rate of iodine formation due to the photodecomposition of ethyl iodide. A large (500 millicurie radium–beryllium) source was housed in a cylinder of paraffin wax, on which stood the flask containing the ethyl iodide, which was first purified by shaking it with sodium sulphite solution, separating it, keeping it over calcium chloride, and finally filtering it. After irradiation the iodide was extracted in a separating funnel by shaking for a standard time (30 seconds) with dilute potassium iodide solution, the volume of which was about one-tenth of that of the ethyl iodide. The mixture was allowed to settle for a given time (2·5 minutes), and the denser ethyl iodide run off. It was found advisable to put a small constriction in the outlet of the separating funnel to ensure that droplets of the aqueous extract adhering to the walls were not dragged out with the ethyl iodide.

The aqueous extract, together with the washings from the funnel, was then poured into another separating funnel containing a little carbon tetrachloride. This was shaken to remove any ethyl iodide remaining, as this tends to hydrolyse in hot silver nitrate solution, producing more silver iodide; this is undesirable as it increases unnecessarily the self absorption of the silver iodide layer for the β-particles. The potassium iodide solution was then precipitated with a mixture of 10 c.c. each of 30% nitric acid and 0·5% silver nitrate solutions; it was found necessary to standardize this precipitation since under certain conditions the precipitated silver iodide tends to peptise.

When iodine was added to the ethyl iodide before irradiation, it was extracted with water containing enough sodium sulphite to reduce the iodine to iodide. It was found that a large excess of sodium sulphite was undesirable, as the aqueous extract tended to form an emulsion in the ethyl iodide; sodium hydrogen sulphite and sulphurous acid can also be used instead of sodium sulphite, but then the ethyl iodide tends to dissolve free sulphur dioxide, and has to be purified from it before the next irradiation by extraction with dilute sodium hydroxide solution.

The silver iodide was filtered through a small filter-paper (1 cm. diameter) held in a Gooch crucible, washed with 3% nitric acid, alcohol, and ether, and mounted in a holder which consisted of a brass plate having a central hole (1·1 cm. diameter) one side of which was closed by a piece of cellophane tape (weight 8·3 mg./cm.^{2}). The filter-paper was laid face downwards in the hole so that the silver iodide was in contact with the tape, and held in position by a small brass disc which fitted the hole tightly and was itself fixed by means of another piece of tape. The brass plate fitted a groove in a lead castle and was located so that the centre of the precipitate was under the centre of a G.E.C. " End-on " counter. The latter was held with the wire positive, the Geiger pulses obtained being amplified and passed into a Dynatron scaling unit. Readings were taken every minute, corrected for decay, for the paralysis time of the circuit, and for variation in counting conditions by means of an uranium oxide standard, and the mean of these taken. The errors given are the root-mean-square deviations of the counts obtained.

The reproducibility of the precipitation and measurement was checked by precipitating aliquots of a standard potassium iodide solution (containing radio-iodide ions) and measuring them, the counts obtained falling within the statistical error.

Self-absorption.—A rough " self-absorption " curve (of the β-particles in silver iodide) was obtained by diluting a solution of potassium iodide containing radio-iodide ions, taking aliquots, and precipitating after the addition of various known amounts of potassium iodide. The counts obtained (corrected to a given time) are shown in Table I; from these it appears that no correction for self-absorption was necessary providing that the weight of silver iodide was not greater than 56 mg./cm.^{2}, and that in this region there was little chance of errors due to unevenness of the precipitate.

TABLE I.

Run I.	AgI (mg.)/cm.^{2}.	Counts obtained.	*Run II.*	AgI (mg.)/cm.^{2}.	Counts obtained.
	16	15,500 ± 160		21	2540 ± 50
	38	15,600 ± 150		40	2500 ± 40
	54	15,500 ± 150		56	2570 ± 55
				98	2330 ± 60

Exchange between the Extractable ^{128}I and Inactive Ethyl Iodide.—It was found that exchange occurred at room temperature between the iodine in the extractable species and that in the bulk of the ethyl iodide. Since nearly all the iodine atoms in the latter were inactive, this meant that the rate at which the extractable radio-iodine disappeared was greater than could be accounted for by the decay constant alone, and consequently to correct the activity extracted for " saturation irradiation " (*i.e.*, the state when further irradiation did not result in a greater activity being obtained) the constants of the exchange reaction had to be determined (see later). The rate of exchange was measured by placing ethyl iodide (irradiated for a standard time at room temperature) in a thermostat at the desired temperature until thermal equilibrium was established. The ethyl iodide could then be extracted directly or, in the case of higher temperatures (where evaporation was liable to produce some error), cooled for a short standard time before extraction. The count obtained could then be considered as the activity at t (time) = 0; by varying the duration in the thermostat, the rate of exchange could be determined.

Efficiency of Extraction.—The efficiency of the extraction process for two reagents (potassium iodide solution, and the same solution containing a little sulphite) was obtained by making successive extractions of an irradiated sample of ethyl iodide; the activities obtained are given in Table II. The fact that the first extracts for both reagents are the same (within experimental error) can be explained by assuming that the amount of elementary iodine produced by the recoiling iodine atoms is small compared with the iodide present in the potassium iodide solution (when no sulphite is present). Exchange of the type $I^- + II^* \rightleftharpoons I^{*-} + I_2$ will then ensure that most of the radio-iodine atoms present will move into the aqueous layer (Roginsky and Gopstein, *Physikal. Z. Sowjetunion*, 1935, **7**, 672). It can be seen from Table II that more than one extraction is uneconomical, as in the time required for another extraction the first will have decayed by an amount greater than the activity gained.

The absolute efficiency (*i.e.*, the ratio of the radio-iodine extracted from the irradiated mixture to the total radio-iodine present as HI^*, I_2^*, and $C_2H_5I^*$, $C_2H_4I_2^*$, etc., produced by combination of the recoiling I^* with organic free radicals) was determined by measuring the activities of an unextracted and an extracted sample of ethyl iodide contained in a double-walled vessel. The inner wall of this was made of very thin glass permeable to some of the β-particles and was of such a diameter that it could be placed round a thin-walled cylindrical aluminium counter. The efficiencies observed (from one extraction only) are given in Table III. The significance of the increase in efficiency when the ethyl iodide contains iodine is discussed later.

TABLE II.

Extracting agent.	Extraction.	Activity (referred to a standard time).	Total activity.
KI (0·03%) solution	First	17,200 ± 380	
	Second	671 ± 15	18,300 ± 400
	Third	310 ± 9	
	Fourth	175 ± 6	
KI (0·03%) solution + Na_2SO_3	First	17,400 ± 500	
	Second	616 ± 15	18,100 ± 500
	Third	41 ± 5	
	Fourth	27 ± 3	

TABLE III.

Initial state of EtI.	Extracting agent.	Efficiency = ^{128}I extracted/^{128}I present before extraction.
0·005 g. I_2/l.	Na_2SO_3 soln.	0·657 ± 0·014 0·630 ± 0·010 } mean = 0·643 ± 0·030
No I_2	KI soln.	0·589 ± 0·036 (calc.)

Comparison of Ethyl Iodide with Other Detectors.—Ethyl iodide has been compared with dysprosium and indium as a detector of weak neutron fluxes; the latter are often used owing to their large capture cross-sections for thermal neutrons. The source used was a 10-year old radon–beryllium tube (now a polonium–beryllium tube). The dysprosium was in the form of oxide supported by cellophane tape so that its weight was 40 mg./cm.^{2} and its total area was 15 cm.^{2}. (This corresponded very roughly to the half-value thickness of dysprosium oxide for the absorption of the β-particles from the active isotope produced, *i.e.*, 50 mg./cm.^{2}.) The latter value was calculated from the absorption coefficient in

aluminium (it being assumed that the mass-stopping power for β-particles of the same energy is a constant). The indium was a foil of area 13·5 cm.² and thickness 0·05 cm. (360 mg./cm.²) and was larger than the half-value thickness for the β- and γ-rays emitted by its active isotope (226 mg./cm.²); this quantity was calculated directly by measuring the reduction in activity when a piece of inactive indium foil was placed between an active sample and the counter.

These detectors were irradiated to saturation by placing them round the source in a large bath of water (to slow down the neutrons) and were arranged to fit round a thin-walled (0·13 mm.) cylindrical aluminium counter, the background of which was 8·3 counts/minute in a lead castle 6 cm. thick. Table IV shows the counts obtained for saturation irradiation immediately after removal from the source.

The ethyl iodide irradiations were performed by holding the source at the centre of a round-bottomed soda-glass flask which was filled with ethyl iodide and iodine (0·01 g./l.) and suspended in a water tank; the counts given in Table IV are those obtained for saturation irradiation 25 minutes after removal from the source. The extraction and precipitation, etc., could be achieved comfortably in this time without the use of a centrifuge. Since the amount of radioactive silver iodide could be made as small as desired, the specimen was mounted in a hole in a brass plate 0·15 cm. thick, and supported at both ends with cellophane tape. By sliding this plate between two G.E.C. end-on counters mounted with their windows facing each other and about 0·3 cm. apart, the counts obtained were double those from the arrangement described above. The background of the counters (15·5 counts/minute in a lead castle 6 cm. thick) was approximately twice that due to a single counter, but since the percentage statistical error is given by $100\sqrt{N_s + N_b}/(N_s - N_b)$, where N_s is the number of counts due to the specimen and background, and N_b the number due to background only (for the same period), the statistical error given by this arrangement is $1/\sqrt{2}$ of that obtained using a single counter.

In Table IV the results given are for saturation irradiation; to attain a given degree of saturation, the time of irradiation for ethyl iodide is appreciably shorter than for the other detectors, a fact which may prove important when the neutron flux to be measured is of short duration.

Since iodine has a resonant absorption for 36 electron-volt neutrons, it is almost impossible to calculate the variation of the activity obtained with volume of the ethyl iodine when the neutron flux is not wholly thermal, and consequently some experimental figures for this are also included in Table IV.

TABLE IV.

(All detectors irradiated to saturation.)

Detector.		Counting time (mins.).	Total counts.	Counts due to back-ground.	Counts due to detector.	Statistical error, %.
Dy_2O_3 (2·5 hrs. half-life)		30	340	249	91 ± 24	26·3
		150	1,600	1245	355 ± 53	14·9
		300	3,020	2490	530 ± 74	14·0
In (54 mins. half-life)		30	391	249	142 ± 25	17·8
		120	1,344	995	349 ± 49	14·2
		150	1,623	1245	378 ± 53	14·2
	Litres.					
C_2H_5I (25 mins. half-life)	2·70	30	6,575	465	6,110 ± 84	1·37
	2·70	90	11,615	1395	10,220 ± 114	1·11
	1·65	30	6,115	465	5,650 ± 81	1·45
	1·10	30	5,320	465	4,855 ± 76	1·55
	0·51	30	3,590	465	3,125 ± 64	2·05
	0·32	30	2,170	465	1,705 ± 51	3·01

DISCUSSION.

Reproducibility.—By following the extraction process given above, two reproducible methods of extraction were developed. The first was to extract the irradiated ethyl iodide (containing no iodine) with dilute (0·03%) potassium iodide solution. The results given in Table V correspond to the activities obtained immediately after removal from the neutron source and are corrected to saturation irradiation. From the figures given, the experimental error was estimated to be about $\pm 0{\cdot}5\%$. When this method is used, care must be taken to remove all iodine, because the latter reduces the amount extracted owing to exchange with the potassium iodide in the extraction process and also alters the exchange-rate of the extractable radio-iodine with that in the ethyl iodide (see later). Sulphur dioxide and organic bases present in the ethyl iodide are also undesirable, for in the presence of these substances some of the radio-iodine appears on the walls of the irradiation flask, which must then be washed out. With ethyl iodide purified from these substances the amount of radio-iodine left on the walls is negligible (about 0·1—0·2%).

The second method uses a sodium sulphite extraction of an irradiated iodine–ethyl iodide solution. The activities (Table VI*a*) were obtained under the same irradiation conditions as

those in Table V; the significance of the increase in activity when iodine is added is discussed later. By using a set-up nearer the radium–beryllium source and reducing the volume of the ethyl iodide, the independence of the activity obtained with the variation of iodine concentration could be extended over a greater range.

TABLE V.

Counts/min. from KI extractions of pure EtI.	Counts/min. from KI extractions of pure EtI.	Counts/min. from KI extractions of pure EtI.
3633 ± 60	3630 ± 70	3685 ± 70
3701 ± 40	3675 ± 70	3775 ± 70
3703 ± 45	3809 ± 80	
		Mean 3701

TABLE VI.

(*a*)	I_2, g./l.	0·008	0·008	0·012	0·016
	Counts/min. ...	4150 ± 40	3910 ± 70	4050 ± 60	3950 ± 45
					Mean 4015
(*b*)	I_2, g./l.	0·200	0·080	0·020	
	Counts/min. ...	1670 ± 25	1681 ± 24	1661 ± 25	

Exchange.—Since effectively all the iodine atoms in the ethyl iodide after irradiation are inactive, the exchange rate (measured by the fall in activity of the extractable species) will be proportional to the number of radioactive extractable atoms in the ethyl iodide, *i.e.*, $dN/dt = -kN$ (N = number of "extractable" radioactive molecules). The rate of disappearance of extractable iodine atoms due to decay and exchange will be given by $dN/dt = -(\lambda + k)N$, where λ is the decay constant of ^{128}I, and if the activity extracted at $t = 0$ is N_0, and at time t is N_t, then $\ln (N_0/N_t) = (k + \lambda)t$. The results obtained at different temperatures are given in Table VII; the errors in the values of k (the fraction exchanged per min., obtained by subtracting λ from the slopes of curves of $\log N_0/N_t$ against t) were estimated graphically. A trace of ethyl alcohol (normally removed in the drying process) added to the ethyl iodide did not alter the exchange rate at room temperature.

TABLE VII.

Temp.	Time (mins.).	Counts/min.	N_0/N_t.	k.
		(*a*) *No iodine present.*		
0°	0	1449 ± 10	—	
0	47	375 ± 8	3·86 ± 0·10	0·0006 ± 0·0004
0	92	107 ± 1·7	13·55 ± 0·27	
17	0	3700 ± 60	—	
17	31	1419 ± 30	2·61 ± 0·27	
17	70	449 ± 5·1	8·25 ± 0·20	0·0025 ± 0·0005
17	127	79 ± 1	48·25 ± 1·25	
42	0	1109 ± 15	—	
42	29	284 ± 3	3·90 ± 0·10	0·0240 ± 0·0031
42	60	54 ± 1	20·50 ± 0·70	
55	0	41·6 ± 1	—	
55	5	13·2 ± 1·5	3·16 ± 0·50	0·1800 ± 0·0250
55	10	5·02 ± 0·7	8·30 ± 1·50	
		(*b*) 0·01 *G. of iodine per l. of ethyl iodide.*		
0	0	2960 ± 30	—	
0	63	495 ± 5	5·99 ± 0·11	0·0003 ± 0·0003
0	117	108 ± 2	27·41 ± 0·81	
15	0	3960 ± 32	—	
15	79	404 ± 6	9·81 ± 0·21	0·0009 ± 0·0003
15	120	134 ± 2	29·55 ± 0·24	
41	0	2800 ± 19	—	
41	47	694 ± 7	4·03 ± 0·08	0·0021 ± 0·0004
41	109	111 ± 2·5	25·22 ± 0·78	
55	0	1945 ± 19	—	
55	48	415 ± 5	4·69 ± 0·11	0·0041 ± 0·0003
55	76	177 ± 4	10·96 ± 0·35	

By equating $k = \alpha \exp(-E/RT)$, where α is a constant and E the heat of activation of the exchange, and plotting k against $1/T$, one obtains 19 ± 1 kcals./g.-mole for the heat of activation without iodine, and 7·8 ± 1·5 kcals./g.-mole in the presence of iodine. The former

value is in good agreement with that obtained by McKay (*J. Amer. Chem. Soc.*, 1943, **65**, 702) for the exchange of iodide ions with ethyl iodide; this suggests that the exchange occurring in pure ethyl iodide is $HI^* + C_2H_5I \longrightarrow C_2H_5I^* + HI$. The mean values of α for the two exchanges are $4{\cdot}56 \times 10^{11}$ and $6{\cdot}46 \times 10^{8}$, respectively; the low value of the latter suggests that perhaps some additive complex of iodine with hydrogen iodide may be formed (*e.g.*, HI_3), in which event steric effects may reduce the exchange rate. An alternative explanation (that the exchange $HI^* + I_2 \rightleftharpoons HI + II^*$ occurs rapidly and is followed by exchange of the radio-iodine with ethyl iodide) can be excluded by Hull, Shifflett, and Lind's observation (*ibid.*, 1936, **58**, 535) that no exchange could be observed between iodine and ethyl iodide at 90°.

The importance of these exchanges on the reproducibility of the extractions can be seen from the following argument. Under the conditions of the experiments, the rate of formation of extractable radio-iodine is a constant, but the rate at which it effectively " decays " is proportional to the decay constant added to the exchange constant k. Assuming that the ethyl iodide is not irradiated long enough for " saturation irradiation " to occur, a correction of the form

$$\text{Activity at saturation} = \frac{\text{Activity immediately after removal from source (calc.)}}{1 - 2^{-t/\tau}}$$

where t = irradiation time, and τ = " effective " half-life, must be applied; τ is given by $\tau = (\ln 2)/(\lambda + k)$.

Although the conditions of irradiation were different from those under which the exchange curves were obtained (owing to γ-rays and free radicals produced by the capture of neutrons), these did not appear to affect (within experimental error) the exchange rate observed, since samples of ethyl iodide which had been irradiated to " half-saturation " (*i.e.*, so that the activity obtained was a half of that at " saturation ") when corrected as above gave activities within 1% of those obtained for " saturation-irradiation." Under very strong γ- or neutron-irradiation however, there might be an increased exchange, and then the above corrections would be invalidated (Williams, *J. Phys. Colloid Chem.*, 1948, **52**, 603).

From the exchange curves observed, it appears that a possible reason for the greater activity obtained when iodine is added to the ethyl iodide is that at saturation the equilibrium concentration (under constant irradiation conditions) will be greater since the exchange is much reduced. Using this reasoning, at saturation:

number of " extractable " I^* atoms produced/min. = − number " decaying "

$$= -\,3701\,(\lambda + k_1) \text{ (No } I_2 \text{ present)}$$

$$= -\,N_1\,(\lambda + k_2) \text{ } (I_2 \text{ present})$$

where N is the activity expected from iodine–ethyl iodide solutions. (The number of counts due to the added iodine at the concentration used, 0·01 g. of iodine per l. of ethyl iodide, is very small compared to those due to the ethyl iodide, and can be neglected.) Substituting for k_1, k_2, and λ, N_1 is found to be 3915 ± 165, in fair agreement with the observed value (4015 ± 70). This means that the chief function of iodine is to inhibit the exchange, and not, as might have been expected, to increase the efficiency of the γ-recoil process by exchange of the type I^* (recoiling) $+ I_2 \longrightarrow II^* + I$, thus reducing the chance of recombination of the recoiling atom with a free radical; this is also substantiated by the fact that the activity extracted is independent of concentration of elementary iodine in the ethyl iodide.

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265. *Deoxy-sugars. Part I. The Dische Reaction for 2-Deoxypentoses.*

By R. E. Deriaz, M. Stacey, Ethel G. Teece, and L. F. Wiggins.

The nature of the reaction between the Dische reagent (diphenylamine in acetic and sulphuric acids) for deoxyribonucleic acid and 2-deoxy-sugars has been investigated. The reaction is shown to depend upon the conversion of the 2-deoxypentose under acid conditions into ω-hydroxylævulic aldehyde which then reacts with diphenylamine to give a mixture of solid complexes, some of which under acid conditions give a typical blue coloration and a characteristic absorption band. Numerous carbohydrate derivatives studied under the conditions of the reaction give well-defined absorption bands which serve to establish the specificity of the Dische reaction.

Dische (*Mikrochemie*, 1930, **8**, 4) describes a reagent consisting of a mixture of diphenylamine, acetic acid, and concentrated sulphuric acid which on being heated with solutions of deoxyribonucleic acid under carefully controlled conditions gives an intense blue coloration. When suitable concentrations of deoxyribonucleic acid were used (*e.g.*, 0·02—0·2%) the intensity of the blue colour appeared to be proportional to the amount of the deoxyribonucleic acid present. The method was adopted by Sevag, Smollens, and Lackmann (*J. Biol. Chem.*, 1940, **134**, 523) for the determination of deoxyribonucleic acid in cellular material.

The specificity of the Dische reaction is based on the fact that deoxyribonucleic acid contains 2-deoxyribose, for it is this carbohydrate component which is responsible for the reaction with diphenylamine to give the blue coloration. However, Pirie (*Brit. J. Exp. Path.*, 1936, **17**, 269) and others have emphasized that great care must be taken in interpreting the results of the test inasmuch as other substances present may interfere with the reaction. For example, agar and the carbohydrate of carragheen moss (which may contain *aldehydo*-sugars) give somewhat similar colours and other complex carbohydrates such as ovomucoid may also give interfering colour re ctions.

In view of the important rôle which deoxyribonucleic acid plays in the nucleal material of cells (Mirsky and Pollister, *Proc. Nat. Acad. Sci.*, 1942, **28**, 344; Mirsky, "Advances in Enzymology and Related Subjects," Interscience Publishers, New York, 1943, **3**, 1; Avery, McLeod, and McCarty, *J. Exp. Med.*, 1944, **79**, 137) and hence of the necessity for its detection and its accurate estimation, and more particularly the need for its differentiation from ribonucleic acid (spectrographic analysis failing to distinguish between the two acids), it seemed desirable to examine this reaction in detail and to determine whether the blue coloration was in fact due to the reaction of deoxyribose itself or to some transformation or decomposition product thereof. It was clearly desirable also to determine the origin of similar colorations which might be obtained when using other types of carbohydrate. Accordingly, a large number of carbohydrate and aldehydic substances were submitted to the precise conditions of this test and the results obtained could be classified into several groups according to the coloration produced (see Experimental section, Table I, etc.).

The following were typical: (*a*) Aldohexoses, aldohexose derivatives, and aldopentoses, *e.g.*, glucose, galactose, mannose, glucose-1 phosphate, glucose-6 phosphate, maltose, arabinose, and xylose; these substances gave *no coloration*. (*b*) Aldehydes, *e.g.*, benzaldehyde, salicylaldehyde, piperonal, furfuraldehyde, hydroxymethylfurfuraldehyde; these gave a *green coloration*, whereas acetaldehyde and cinnamaldehyde gave *brown colours*. (In these tests with liquid aldehydes the concentration of the aldehyde was probably greatly in excess of the prescribed amount of 10 mg. because 1 drop was used). (*c*) Ketoses, *e.g.*, fructose, sucrose, and sorbose, gave *green colorations*. (*d*) Hexals, *e.g.*, lactal, triacetyl glucal, and galactal, gave a *pink-violet coloration*. (*e*) Thymonucleic acid, 2-deoxy-D- and -L-ribose, D- and L-arabinal, and furfuryl alcohol gave the intense *characteristic blue coloration*. (*f*) Lævulic acid (as I) which is the final common acid-hydrolytic product of 2-deoxyribose, arabinal, and furfuryl alcohol, gave *no coloration*.

These preliminary tests showed that, in addition to thymonucleic acid, 2-deoxy-L-ribose (IV), L-arabinal (V), and furfuryl alcohol (III) also give the typical blue coloration. It was clearly desirable to discover the underlying reason for the fact that such structurally dissimilar compounds could exhibit a similarity of behaviour with this reagent. It seemed probable that the substance actually responsible for the coloration was some common acid degradation product which could be produced from all four of these substances, and such a common product is lævulic acid. However, the negative test given by this acid showed that it could not be the

colour-producing intermediate, so it was decided that an aldehyde precursor might be responsible and the isolation of such a substance was therefore attempted.

When we observed that furfuryl alcohol gave the characteristic blue colour in the Dische test, we noted that for some time it has been known that furfuryl alcohol can be converted by treatment with methyl-alcoholic hydrogen chloride into the dimethyl acetal of ω-methoxylævulic aldehyde (II), and that this moreover on further hydrolysis with methanolic hydrogen chloride can be transformed into methyl lævulate (I) (see Pummerer and Gump, *Ber.*, 1923, **56**, 999; Pummerer, Guyot, and Birkofer, *Ber.*, 1935, **68**, 480). It was therefore decided to prepare this aldehyde and to investigate its behaviour under the conditions of the Dische reaction.

Accordingly (III) was boiled for 3 hours with methanolic hydrogen chloride (0·1%) (Pummerer and Gump, *loc. cit.*) and thereby was converted into the acetal (II) (a colourless liquid) which was characterised by formation of the crystalline *bis*-2 : 4-*dinitrophenylhydrazone* of the aldehyde. ω-Hydroxylævulic aldehyde or its derivatives, under the conditions of the Dische reaction, did indeed give the characteristic blue coloration, and quantitative measurements on the Spekker photoelectric absorptiometer (described below) showed that the intensity of the colour was slightly greater than that given by equivalent weights of (III), (IV), (V), or deoxyribonucleic acid.

Attempts were next made to convert both 2-deoxyribose and arabinal into (II). L-Arabinal with 0·1% methanolic hydrogen chloride was readily converted into (II), which was identified as before by formation of its bis-2 : 4-dinitrophenylhydrazone. On the other hand, 2-deoxyribose with 0·1% methanolic hydrogen chloride gave, not (II), but a new crystalline methylglycoside of 2-deoxyribose, which will be described in detail in a later communication. From its behaviour on acid hydrolysis it appeared to be β-methyl-2-deoxyribopyranoside and it also gave the characteristic blue colour on being treated with the Dische reagent.

Under more drastic conditions such as obtain when 2-deoxyribose was heated under pressure with 0·1% methanolic hydrogen chloride at 180°, a mixture of methyl lævulate and (II) was obtained. Separation of the two liquids was effected by treatment of the mixture with 10% methanolic potassium hydroxide, by means of which the methyl ester was hydrolysed and the unaffected (II) was then extracted by ether. It was identified as previously described.

It is thus established that 2-deoxyribose, arabinal, and furfuryl alcohol are all convertible into one and the same degradation product, namely ω-methoxylævulic aldehyde, isolated in the form of its dimethyl acetal (II). Attempts to obtain the same compound directly from thymus deoxyribonucleic acid were, however, not successful, although after treatment with methanolic hydrogen chloride and distillation of the product a liquid was obtained which did give a positive Dische reaction and probably contained (II).

With another colleague, we have obtained from sperm deoxyribonucleic acid, a deoxyribose derivative of thymine which does indeed yield ω-hydroxylævulic aldehyde on acid treatment.

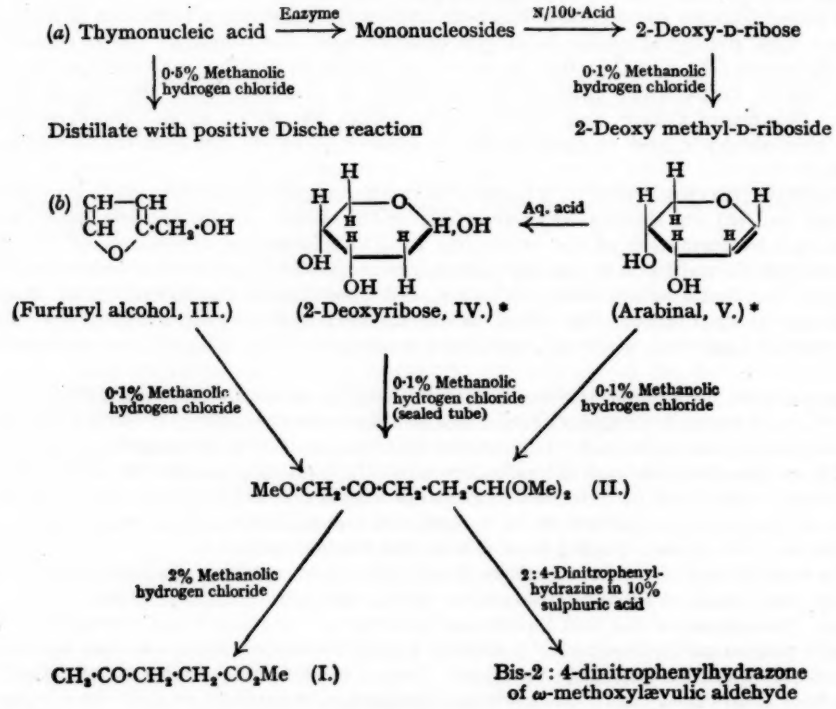
The main reactions are summarized on p. 1224.

In view of the importance of deoxyribonucleic acid in natural products and of the need for its accurate detection and determination, the specificity of the Dische reaction has been further examined quantitatively by a study of the absorption curves of the coloured reaction products obtained by heating a wide variety of carbohydrate derivatives with the reagent.

In each case highly purified specimens of the various substances were used and the following experimental procedure was adopted so that exactly comparable results were obtained. The Dische reagent (6 c.c.) was mixed with water (3 c.c.) containing a known weight of the substance to be tested (final concentration of substance, 0·02—1·0 mg./c.c.), and the mixture heated in a standard test-tube in a briskly-boiling water-bath (3·25 min.). After exactly 15 minutes' cooling in ice-water, the absorption was measured immediately in a Spekker absorptiometer, and the absorption curve obtained by plotting ε against λ, where ε is the molecular extinction coefficient [*i.e.*, I (Spekker reading) $\times$ M/conc. (in g./l.)], and λ is the wave-length of the light transmitted. It was found that the substances tested could be divided sharply into four classes (Figs. 1—4), as follows.

(1) *Substances giving the characteristic blue coloration.* Deoxyribose derivatives and related compounds gave absorption curves showing a characteristic band with the maximum at λ 5800 (see Fig. 1) identical with that given by (II). These results are in accordance with the view given previously that the compound responsible for the characteristic blue coloration is ω-hydroxylævulic aldehyde and that only those substances which can be transformed into this compound will give a positive specific reaction. From Fig. 1 it is seen that of all the substances examined ε is greatest for the keto-acetal (II) and that D- and L-arabinal and furfuryl alcohol, which are more

easily converted into the keto-acetal than is 2-deoxyribose, show a greater intensity of colour than the latter, whereas on the other hand stable glycosidic derivatives of deoxyribose show a



diminished value for ε. It is of interest that dimethyl β-methyl-2-deoxy-L-ribopyranoside shows a much lower value of ε than do the other derivatives—a result which can now be expected in

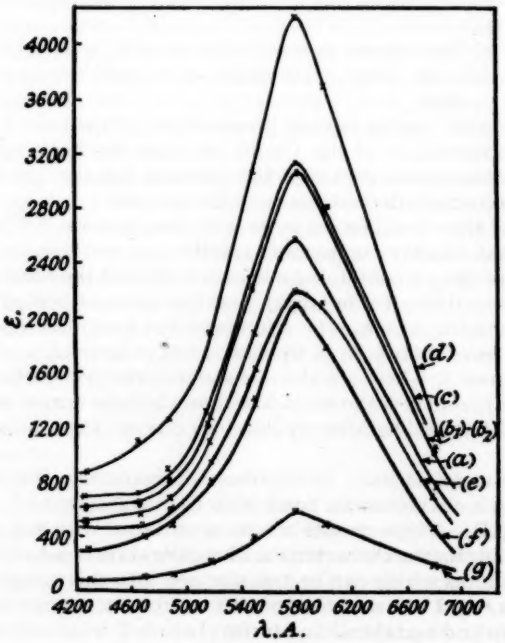


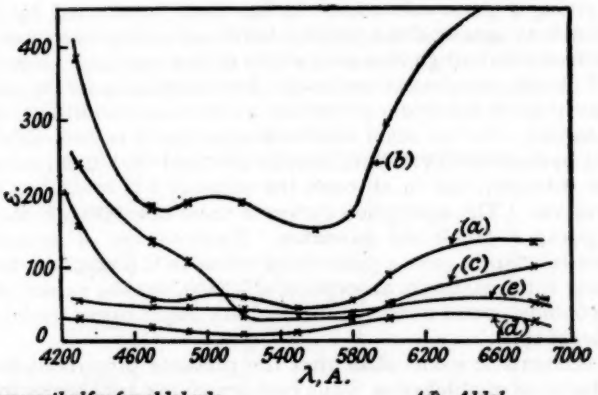
FIG. 1.

(*a*) *2-Deoxy-D-ribose.*
(b_1) *D-Arabinal.*
(b_2) *L-Arabinal.*
(*c*) *Furfuryl alcohol.*
(*d*) *ω-Methoxylævulic aldehyde dimethyl acetal.*
(*e*) *Sodium thymonucleate.*
(*f*) *β-Methyl-2-deoxy-L-ribopyranoside.*
(*g*) *Dimethyl derivative of* (*f*).

* For convenience, formulae (IV) and (V) have been written as the D-isomers although the reactions described were carried out with the L-isomers.

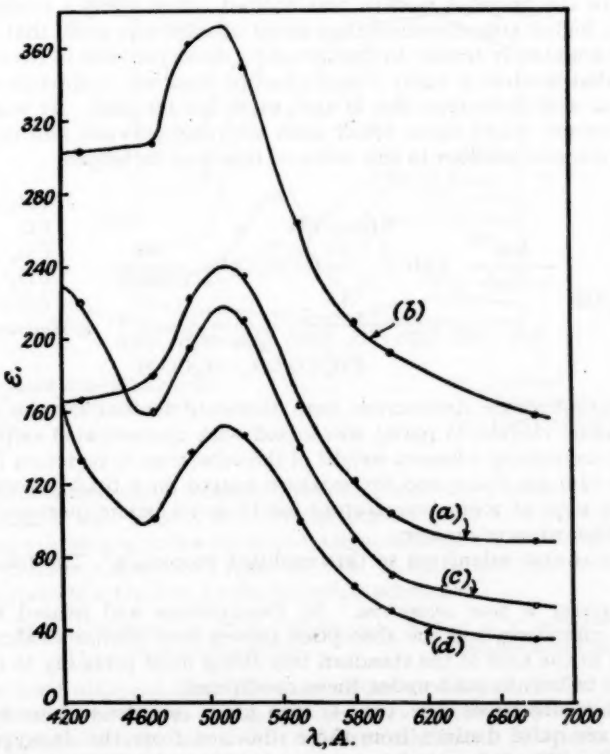
that the transformation of this compound into ω-hydroxylævulic aldehyde would be much more difficult inasmuch as it involves the cleavage of an ether methyl group. Other derivatives

FIG. 2.



(a) *Hydroxymethylfurfuraldehyde.*
(b) *Bis-(2-furfurylmethyl) ether.*
(c) *Tetra-acetyl oxyglucal.*
(d) *Aldol.*
(e) *Glyceraldehyde.*

FIG. 3.



(a) *Lactal.*
(b) *Triacetyl glucal.*
(c) *Hexa-acetyl lactal.*
(d) *Hexa-acetyl maltal.*

which gave a positive result in this reaction were α-methyl-2-deoxy-L-ribopyranoside, αβ-methyl-2-deoxy-D- and -L-ribofuranosides, dimethyl αβ-methyl-2-deoxy-L-ribofuranoside, 2-deoxy-D-ribose anilide, and β-2-deoxy-D-ribose penta-acetate.

(2) *Substances giving no interfering coloration.* It was established that the following

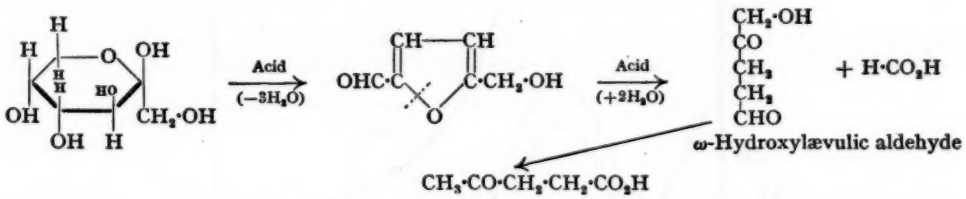
substances gave no colour in the given concentrations (mg./c.c.) and that the colours given with concentrations 10 times these quoted do not interfere in this reaction: Glucose (0·16), arabinose (0·13), maltose (0·26), lactose (0·3), fructose (0·23), sucrose (0·37), sorbose (0·3), ascorbic acid (0·18), acetaldehyde (0·2), formaldehyde (0·2), benzaldehyde (0·2), acetone (0·2), lævulic acid (0·3).

(3) *Substances giving a green coloration.* It has been mentioned by Pirie (*loc. cit.*) that certain substances such as agar and the polysaccharide of carragheen moss which may contain *aldehydo*-sugars produce interfering green colorations in this reaction. However, in experiments carried out with 3 : 6-anhydroglucose and with 3 : 6-anhydro-α-methylmannoside, which, as the free sugars, may possess aldehydic properties under some conditions, only very pale green colorations were obtained. On the other hand, examination of certain aldehydes such as aldol, glyceraldehyde, and hydroxymethylfurfuraldehyde revealed that these substances give a green coloration of higher intensity, but in all cases the value of ε is much less than that shown by deoxypentose derivatives. The absorption curves in these cases (Fig. 2) show no striking band.

(4) *Substances giving a pink-violet coloration.* Examination of several hexal derivatives showed that all these substances gave a pink-violet colour in this reaction, the absorption curves (Fig. 3) having a band with maximum absorption at λ 5100, but the values of ε were much lower than for the corresponding pental series. This reaction might prove useful for the detection of derivatives of the hexal type.

From these experiments it seems clear that the presence of carbohydrate derivatives and decomposition products, or of aldehydes, while perhaps giving apparently interfering coloration during superficial examination in the test-tube, is unlikely to affect the comparative results of deoxyribose estimations if the experimental procedure is rigidly applied with suitable concentrations of material and with careful determination of light-absorption data.

In the course of the previous work it was noticed, when using a modified Dische reagent which contained a higher concentration than usual of sulphuric acid, that certain keto-sugars gave a blue colour apparently similar to that given by deoxypentoses in the standard test. It is known, however, that fructose is easily transformed by acid into hydroxymethylfurfuraldehyde and that on further acid hydrolysis this in turn gives lævulic acid. It was thought therefore that the blue coloration might again result from ω-hydroxylævulic aldehyde which might be formed as an intermediate product in this series of reactions as follows:



Various keto-carbohydrate derivatives were therefore treated by the following modified procedure; the Dische reagent (5 parts) was mixed with concentrated sulphuric acid (1 part) and water (3 parts) containing a known weight of the substance to be tested (final concentration of substance, 0·02—1·0 mg./c.c.), and the mixture heated on a briskly-boiling water-bath for 5 minutes and then kept at room temperature for 15 hours before measurement of the colour intensity on a Spekker absorptiometer.

2-Deoxyribose was also submitted to this modified procedure. The following results were obtained.

(1) *Substances giving a blue coloration.* (*a*) Deoxyribose and related substances gave a characteristic blue coloration, and the absorption curves were similar to those shown in Fig. 1 but ε was less than in the case of the standard test owing most probably to rapid hydrolysis of some deoxypentose to lævulic acid under these conditions.

(*b*) The following substances (see Fig. 4) also gave an intense blue coloration but the absorption curves are quite distinct from those obtained from the deoxypentose derivatives and show two bands with maximum absorption at λ 5200 and λ 6300 approx.

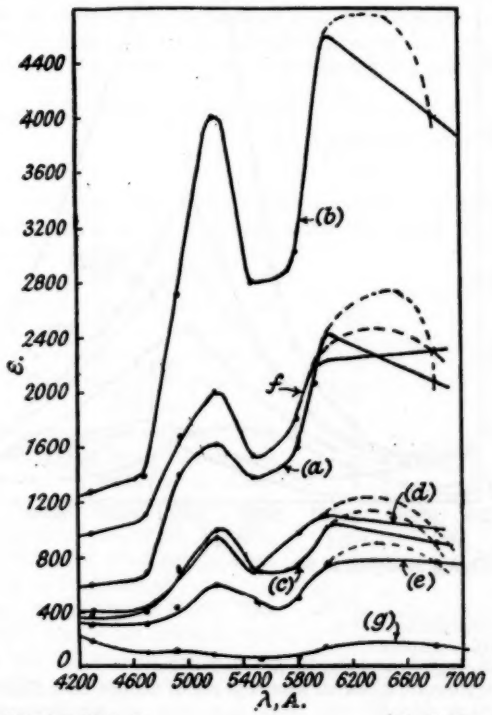
It is seen from Fig. 4 that hydroxymethylfurfuraldehyde and the related bis-(2-furfurylmethyl) ether give absorption curves of the same shape as that obtained with ketohexoses, although with the first two substances ε has a greater value. It is therefore probable that in this reaction ketohexoses decompose to give hydroxymethylfurfuraldehyde and that this then reacts with the diphenylamine reagent. There is no clear indication of the formation of the keto-acetal (II) in this reaction. It is possible that this reaction could provide a useful method

for the detection of ketoses, and a comparison of ε at λ 5200 might be developed as a method of determination for keto-sugars.

(2) *Substances giving a green coloration.* Certain aldehydes such as aldol and furfuraldehyde give green colorations in this reaction but in all cases the value of ε is extremely low (see Fig. 4, Curve *g*, for furfuraldehyde).

(3) *Substances giving no coloration.* The following substances gave no coloration in this reaction : glucose (0·3 mg./c.c.), arabinose (0·14), lactose (0·3), ascorbic acid (0·18), acetaldehyde (0·2), benzaldehyde (0·2), formaldehyde (0·2), acetone (0·2).

FIG. 4.



(*a*) *Hydroxymethylfurfuraldehyde.*
(*b*) *Bis-(2-furfurylmethyl) ether.*
(*c*) *Fructose.*
(*d*) *Sucrose.*
(*e*) *Sorbose.*
(*f*) *Tetra-acetyl oxyglucal.*
(*g*) *Furfuraldehyde.*

A comparison of diphenylamine oxidation products with the products of the Dische reaction was now made, for it is well known that diphenylamine gives a blue-purple coloration when treated with certain oxidising agents such as potassium dichromate in acid solution. It has been shown (see Knop, *J. Amer. Chem. Soc.*, 1924, **46**, 263; Kolthoff and Sarver, *ibid.*, 1930, **52**, 4179) that the reaction proceeds according to the following scheme :

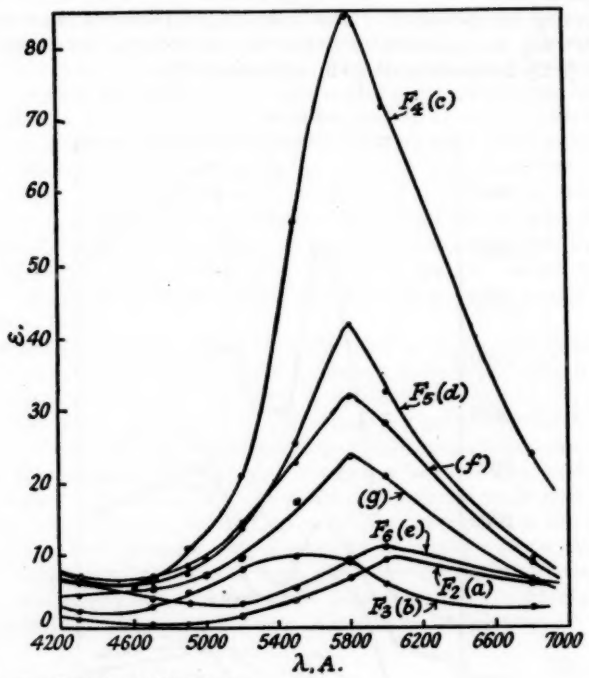
$$2NHPh_2 \xrightarrow{-H_2} \underset{\text{Diphenylbenzidine.}}{NHPh\cdot C_6H_4\cdot C_6H_4\cdot NHPh} \rightleftharpoons \underset{\text{Diphenylbenzidine-violet.}}{NPh{:}C_6H_4{:}C_6H_4{:}NPh} + 2H^+ + 2\varepsilon$$

It might have been objected that the blue colour developed in the Dische reaction was related to diphenylbenzidine-violet, so this substance was prepared (see p. 1231) and two series of absorption measurements were taken with different solutions. It was found that the general character of the curves was similar to that shown by the blue of the Dische reaction; diphenylbenzidine-violet, however, had the maximum at λ 5500 instead of λ 5800. When diphenylbenzidine was put into acid of the same concentration as that of the Dische reagent it gave a curve with maximum at λ 5800. However, this blue colour was unstable to heat and disappeared on standing, whereas the colour given with the Dische reagent was quite stable and only changed in intensity over long periods of time.

The ultra-violet absorption of diphenylbenzidine-violet was compared with that given by

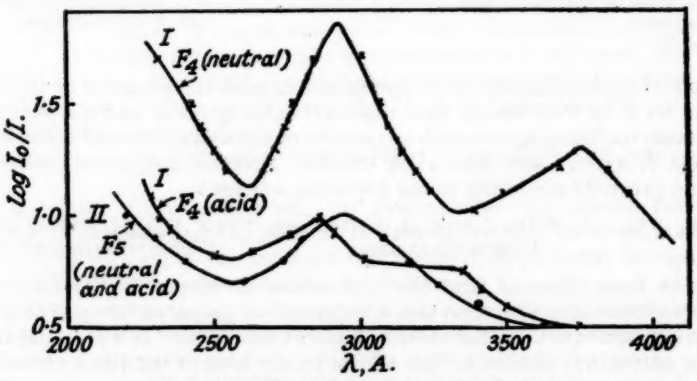
fraction F_4, the true "Dische" blue fraction actually isolated as described below from the products of the Dische reaction (Fig. 6): F_4 shows two bands, λ 2960 (log $I_0/I = 1{\cdot}9$) and λ 3750 (log $I_0/I = 1{\cdot}3$), in neutral solution, and one band, λ 2850 (log $I_0/I = 1{\cdot}0$), in acid

FIG. 5.



(*a*) F_2, *aq. alcohol acidified to* 5N.
(*b*) F_3, " " " "
(*c*) F_4, " " " "
(*d*) F_5, *neutral alcohol.*
(*e*) F_6, *acidified alcohol.*
(*f*) *Furfuryl alcohol (heated with Dische reagent).*
(*g*) *ω-Methoxylævulic aldehyde dimethyl acetal (heated with Dische reagent).*

FIG. 6.



Ultra-violet absorption spectra of F_4 and F_5.

solution. On the other hand, diphenylbenzidine-violet shows no band between λ 2300 and λ 4500.

For the following reasons we consider that the blue coloration of the Dische reaction is not identical with diphenylbenzidine-violet: (*a*) In the Dische reaction there is a very great excess

of diphenylamine necessary for production of the blue colour, so it would not be possible for the oxidation reaction to take place, for insufficient oxygen would be present to produce diphenylbenzidine-violet. (*b*) The Dische colour appears to be stable on being kept or on being heated, whereas diphenylbenzidine-violet is unstable to heat and disappears on being kept. (*c*) The ultra-violet spectrum differs from that of F_4 obtained from the Dische reaction as described below.

Finally, we have attempted the isolation of the actual substance responsible for the blue colour in the Dische reaction. It has been suggested by Cohen (*J. Biol. Chem.*, 1944, **138**, 691) that condensation of secondary amines with aldohexoses, aldopentoses, or aldehydes of the type CHO·CH(OH)·R″ does not result in the formation of coloured products because these substances can participate in the Amadori reaction (*Atti R. Accad. Lincei*, 1925, **2**, 337; 1931, **13**, 72, 195), the course of the reaction then proceeding to the ketone (*C*), in which the length of the conjugated system is not increased. With deoxypentoses and substances of the type $CHO{\cdot}CH_2R''$, however, the reaction cannot proceed beyond stage (*B*), thus increasing the number of conjugated double

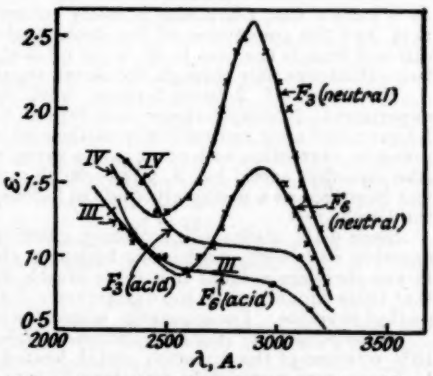
$$NHRR' + OCH{\cdot}CHR''{\cdot}OH \longrightarrow \underset{(A.)}{\overset{+}{N}RR'{:}CH{\cdot}CHR''{\cdot}OH} \xrightarrow{-H^+} \underset{(B.)}{NRR'{\cdot}CH{:}CHR''{\cdot}OH} \longrightarrow \underset{(C.)}{NRR'{\cdot}CH_2{\cdot}COR'}$$

bonds, particularly if R″ also contains a conjugated system. The specificity of a special tryptophan reaction for deoxypentoses is ascribed to the formation of compounds of this type (Cohen, *loc. cit.*). It was also suggested that the reddish-purple colour obtained by treatment of deoxyribose with the Dische reagent at room temperature is due to a similar condensation, whereas the blue coloration obtained on heating was thought to involve a more complex series of reactions.

For this reason we examined quantitatively the reddish-purple colour produced by deoxyribose and the Dische reagent in the cold. The curves obtained (*a*) after 24 hours and (*b*) after 48 hours showed that maximum absorption again took place at λ 5800, and it was therefore clear that the reaction follows the same course in the cold as on heating.

In order to gain further information on this question an attempt was made to isolate the substance responsible for the blue coloration and to investigate its properties. The method used was to treat either 2-deoxyribose or arabinal with the Dische reagent in the usual way. The sulphuric acid was neutralised with barium acetate, and the coloured products separated from the filtered concentrated liquid by extraction with ether. Separation of the coloured products from unreacted diphenylamine was achieved by means of an alumina chromatogram. A small portion of one fraction gave an intense blue coloration on treatment with acid, and the product in the fraction was obtained in the form of an orange-coloured powder.

FIG. 7.



Ultra-violet absorption spectra of F_3 and F_5.

This material, with several others—fractions F_1—F_6—was made on a larger scale by reaction of furfuryl alcohol with diphenylamine. It was clear that the one fraction (F_4), although obtained in only about 10% yield of the total, was the actual material responsible for the typical blue colour, since it had the absorption band at λ 5800 characteristic of ω-hydroxylævulic aldehyde in the test. Another fraction F_5 actually gave the blue coloration in neutral solvents and possessed a similar absorption curve (see Figs. 6 and 7). However, it is clear that these two fractions are not the main product of the reaction, and the blue coloration obviously cannot be identified with the presence of a single condensation product of the secondary amine.

These results would indicate that the Dische reaction is unlikely to be of high reliability in the absolute quantitative sense even when rigorously applied with the use of the Spekker absorptiometer.

On the other hand, with 2-deoxyribose or the dimethyl acetal as a standard, it is of great value for comparative estimations particularly of 2-deoxyribonucleic acid derivatives.

EXPERIMENTAL.

Preparation of ω-Methoxylævulic Aldehyde Dimethyl Acetal.—(i) *From furfuryl alcohol.* Dry furfuryl alcohol (100 g.) was heated under reflux for 3 hours with 0·1% anhydrous methanolic hydrogen chloride

(11.). After cooling and neutralisation with silver carbonate followed by evaporation of the methanol under diminished pressure, a yellowish-brown liquid (70 g.), b. p. (bath temp.) 65—140°/6 mm., was obtained. Purification by formation of the bisulphite compound, followed by extraction with ether to remove furfuryl methyl ether and decomposition of the bisulphite compound, gave a colourless liquid (43 g.) which distilled over the range 74—120°/6 mm. This was carefully fractionated to give the following colourless liquids: (*a*) 11·2 g., b. p. 80°/6 mm.; (*b*) 4·0 g., b. p. 80—84°/6 mm.; (*c*) 26·2 g., b. p. 84—90°/6 mm. The distillate (*c*) was refractionated 3 times more and finally a colourless liquid (10·8 g.), b. p. 89—90°/6 mm., $n_D^{18°}$ 1·4236 (Found: OMe, 51·6. Calc. for $C_8H_{16}O_4$: OMe, 52·9%), was obtained. This ω-methoxylævulic aldehyde dimethyl acetal in minute amounts gave a positive Dische reaction.

The dimethyl acetal was characterised by its conversion into the *bis*-2 : 4-*dinitrophenylhydrazone* of the aldehyde by treating it with a 1% solution of 2 : 4-dinitrophenylhydrazine in 10% (vol.) aqueous sulphuric acid at 37° for 24 hours. A yellow solid separated, which after four recrystallisations from hot ethyl acetate gave yellow needles, m. p. 221° (Found: C, 44·3; H, 3·43; N, 23·3; OMe, 6·28. $C_{18}H_{18}O_8N_8$ requires C, 44·1; H, 3·67; N, 22·9; OMe, 6·33%).

Treatment of the dimethyl acetal with boiling 2% hydrogen chloride transformed it into methyl lævulate, identified as the 2 : 4-dinitrophenylhydrazone, m. p. 141°.

(ii) *From* L-*arabinal.* After various trial experiments L-arabinal (1 g.) (prepared by the method of Meisenheimer and Jung, *Ber.*, 1927, **60**, 1462) was heated under reflux with 0·1% methanolic hydrogen chloride (10 c.c.) for 3 hours. After neutralisation with silver carbonate followed by evaporation of the methyl alcohol under reduced pressure a colourless liquid, b. p. 96—106° (bath temp.)/6 mm., $n_D^{18°}$ 1·4317, was obtained (0·4 g.) (Found: OMe, 41·2%). This distillate gave a strong Dische reaction. Conversion into the 2 : 4-dinitrophenylhydrazone by the method used in (i) yielded a yellow solid which, after several recrystallisations from ethyl acetate, gave yellow needles, m. p. and mixed m. p. with preparation in (i) 221° (Found: C, 44·5; H, 3·92%).

The isolation of this dimethyl acetal was then attempted from 2-deoxy-L-ribose as starting material. It is known that L-arabinal is easily convertible into 2-deoxy-L-ribose by treatment with N-sulphuric acid, but the conversion of the deoxypentose into the dimethyl acetal was found to be much more difficult than is the case in (i) or (ii) (above), showing, in our opinion, that it is unlikely that these last two substances pass through the deoxy-sugar stage in their conversion into the keto-acetal.

Treatment of 2-*Deoxy*-L-*ribose with* 0·1% *Methanolic Hydrogen Chloride.*—In a preliminary experiment, 2-deoxy-L-ribose was heated with 0·1% methanolic hydrogen chloride under reflux for 3 hours, and after neutralisation of the acid and removal of the methanol by evaporation under reduced pressure, extraction with ether gave a syrup which failed to yield any distillate of b. p. below 110°/6 mm. (the dimethyl acetal has b. p. 89—90°/6 mm.), but which crystallised on being kept. This substance was identified as a methylglycoside of 2-deoxy-L-ribose, and it also gave the characteristic blue colour in the Dische test.

Since 0·1% methanolic hydrogen chloride failed to disintegrate the sugar ring, the experiment was repeated with 0·6% methanolic hydrogen chloride but the same glycosidic product was still obtained. It was therefore evident that more drastic methods of hydrolysis were needed, but it was also essential that these should not be too drastic since the dimethyl acetal if formed would be directly converted into methyl lævulate. Consequently, some efforts were made to determine the stability of the acetal.

Decomposition of ω-*Methoxylævulic Aldehyde Dimethyl Acetal with Methanolic Hydrogen Chloride.*—A 10% solution of the dimethyl acetal, heated under reflux with methanolic hydrogen chloride (3%) for 1½ hours, was completely transformed into methyl lævulate, having a negative Dische reaction and identified as the 2 : 4-dinitrophenylhydrazone, m. p. 141°. This experiment showed that it was unlikely that the dimethyl acetal could be isolated by acid hydrolysis at ordinary temperatures and pressures so that sealed tube experiments were then investigated.

In a typical example the dimethyl acetal was heated with 0·1% methanolic hydrogen chloride in a sealed tube at 100°; 65% was destroyed after being heated for 45 minutes. A further rise in temperature seemed to have little effect on the rate of decomposition.

Treatment of 2-*Deoxy*-L-*ribose with* 0·1% *Methanolic Hydrogen Chloride in a Sealed Tube.*—A series of experiments showed that the methylglycoside formed by heating under reflux was still the chief product when the reaction was carried out in a sealed tube at 128—130° for 1½ hours, and that decomposition of the glycoside did not take place until the temperature was raised to 180°. It was therefore evident that a high yield of the dimethyl acetal could not be expected but that the most favourable conditions for the isolation of this substance from L-deoxyribose would be a brief treatment at 180°.

2-Deoxy-L-ribose (3 g.) was therefore heated in a sealed tube with 0·1% methanolic hydrogen chloride (30 c.c.) at 180° for 30 minutes. After neutralisation, removal of the methanol, and extraction with ether, a distillate (0·86 g.), b. p. 85—110°/6 mm., was obtained which gave a positive Dische reaction, but quantitative measurements of the blue coloration and methoxyl determinations revealed that it consisted of methyl lævulate (90%) with only 10% of the dimethyl acetal. Separation of these two substances by means of dilute aqueous sodium hydroxide was impracticable, but a separation was effected by keeping the mixture overnight with methanolic potassium hydroxide (10%) and subsequently refluxing it for 20 minutes. Extraction with ether gave a syrup which gave the bis-2 : 4-dinitrophenylhydrazone, m. p. 221°, shown conclusively by means of an *X*-ray powder photograph to be identical with that prepared from an authentic specimen of ω-methoxylævulic aldehyde dimethyl acetal.

Treatment of Deoxyribonucleic Acid from Thymus Gland with Methanolic Hydrogen Chloride.—So far it has not been possible to obtain deoxyribose from deoxyribonucleic acid by direct chemical methods (*i.e.*, without use of enzymes), the hydrolytic methods necessary to break down the acid into nucleotides resulting in the transformation of the deoxy-sugar into lævulic acid.

Treatment of thymus deoxyribonucleic acid with 0·5% methanolic hydrogen chloride under reflux for long periods showed no dimethyl acetal or glycoside formation, but preliminary experiments using 0·5% methanolic hydrogen chloride in a sealed tube indicated that some decomposition occurred. Finely ground thymus deoxyribonucleic acid (1·3 g.) was therefore heated in a sealed tube with methanolic

hydrogen chloride (8 c.c., 0·5%) for 1 hour at 135°. After neutralisation, removal of the methanol, and extraction with ether, a small amount of distillate, b. p. 60—90°/6 mm., was collected, and this had a positive Dische reaction. By suitable adjustment of experimental conditions it is therefore probable that by this means it will be possible to isolate a methyldeoxyribose or the dimethyl acetal from the nucleic acid.

Preparation of Diphenylbenzidine-violet.—Diphenylamine (0·113 g.) was dissolved in 1 l. of N-sulphuric acid, the solution kept at 50°, and an aqueous solution of potassium dichromate (calculated quantity for the first stage of the reaction on p. 1227) slowly added with brisk stirring. When the addition was complete the solution was boiled and diphenylbenzidine separated as a fine white powder, m. p. 244°. Another equivalent of potassium dichromate was then added and the diphenylbenzidine was converted into diphenylbenzidine-violet. Its ultra-violet absorption was measured on two solutions: (*a*) 0·2 g./l., (*b*) 0·05 g./l. :

(*a*) λ, A.	Spekker reading.	(*a*) λ, A.	Spekker reading.	(*b*) λ, A.	Spekker reading.	(*b*) λ, A.	Spekker reading.
4300	0·372	5500	0·758	4300	0·231	5500	0·492
4700	0·428	5800	0·712	4700	0·270	5800	0·468
4900	0·536	6000	0·579	4900	0·332	6000	0·377
5200	0·646	6800	0·272	5200	0·413	6800	0·192

Condensation of Deoxyribose with the Dische Reagent.—Deoxyribose (*ca.* 2 mg.) was dissolved in water (6 c.c.) and mixed with the Dische reagent (12 c.c.) and the mixture was heated in a boiling water-bath for 3 minutes. After cooling in ice-water the sulphuric acid of the Dische reagent was neutralised by addition of barium acetate solution (2·5 g. in 5 c.c. water). After centrifuging, the solution was extracted several times with ether. By evaporation of the solvent and testing the residue, it was found that the compound responsible for the blue coloration was completely extracted with ether.

Condensation of D-*Arabinal with Diphenylamine.*—A slightly larger-scale experiment was then carried out with D-arabinal as the starting material. D-Arabinal (80 mg.) was dissolved in water (240 c.c.), the solution mixed with the Dische reagent (480 c.c.), and the whole heated in 10-c.c. portions on a boiling water-bath for 3 minutes. After cooling, the solution was freed from sulphate ions, centrifuged, and extracted with ether as before, and the extracts were dried (Na_2SO_4) and evaporated to dryness. Finally, the residue was dissolved in dry benzene, and the solution poured on an alumina column (30 cm. × 1 cm.). The chromatogram was developed by elution with benzene–alcohol (100 : 2, parts by vol.) and the coloured products were retained by the column, the diphenylamine passing through. The fractions of the eluted solution were collected, evaporated to dryness, and tested with acid (5N). One fraction had an intense blue coloration. This gave an orange solution in alcohol and on evaporation of the solvent gave a yellow amorphous solid, soluble in ether and most organic solvents except light petroleum. This yellow solid gave an intense blue coloration with acid of the same composition as used in the Dische reagent.

Condensation of Furfuryl Alcohol with Diphenylamine.—Furfuryl alcohol (0·75 g.) was dissolved in water (500 c.c.) and mixed with a solution of diphenylamine (10 g.) in acetic acid (1 l.) and concentrated sulphuric acid (27·5 c.c.) was added. Portions (100 c.c.) of this solution were then heated separately in a boiling water-bath for exactly 3 minutes and then cooled in ice water and finally combined. Barium acetate (calculated quantity for neutralisation of the sulphuric acid) was then added, the colour of the solution changing from blue to green, and the mixture was extracted three times with ether. The ethereal extracts, which contained excess of diphenylamine, acetic acid, and coloured products, were evaporated under reduced pressure until the water and acetic acid were completely removed. The dark green residue (consisting chiefly of diphenylamine)was dissolved in benzene–light petroleum (b. p. 60—80°) (7 : 3) (50 c.c.), and the solution passed through an alumina column (30 cm. × 1 cm.). The coloured products were absorbed and the diphenylamine was separated by eluting the column successively with benzene–petrol (8 : 2) and benzene–petrol (9 : 1). The coloured products were then removed from the column by elution with absolute alcohol, and the solution evaporated to dryness giving a dark green residue (0·5 g.). This was dissolved in benzene–petroleum (7 : 3), and the column eluted successively with benzene–petroleum (4 : 1), benzene–petroleum (9 : 1), benzene, and benzene–alcohol (200 : 1), and after many refractionations seven principal fractions were obtained and their colour reactions with 5N-sulphuric acid were investigated. The results were as follows :

Fraction.	Weight, mg.	Appearance.	Coloration with 5N-H_2SO_4.
F_1	31·5	Colourless syrup	No coloration
F_2	28·7	Pale yellow syrup	Pale blue-green
F_3	27·5	Yellow syrup	Purple
F_4	29	Yellow amorphous solid	Intense blue
F_5	12·5	Blue amorphous solid	Blue : no change
F_6	88	Yellow-brown solid	Green
F_7	91	Brown solid	Green

Absorption data of fractions F_2—F_6. Each fraction (weighed quantity) was dissolved in a known volume of alcohol, and sufficient acid added to make the solution 5N. After 30 minutes' standing, the absorption was measured on a Spekker absorptiometer and in each case ε (0·1%; 1 cm.) was calculated. The curves thus obtained may well compare with those for furfuryl alcohol and ω-methoxylævulic aldehyde dimethyl acetal on heating with the Dische reagent. The results are shown in Fig. 5, and it is clear that the fraction mainly responsible for the blue coloration is F_4. This substance is a yellow, amorphous, optically inactive solid, very insoluble in water but soluble in most organic solvents except light petroleum; it gives a yellow solution in benzene and a deep orange-yellow solution in alcohol. It behaves as an indicator, giving a yellow coloration in alkali and green in acetic acid, changing to blue about pH 1·5.

F_5, which gives a similar absorption curve, gives a blue solution in neutral solvents and a yellow coloration in alkali, and thus may be closely related structurally to F_4.

Ultra-violet absorption spectra of fractions F_3—F_6. These ultra-violet absorptions have been examined both in neutral and in 5N-acid solution, the concentrations being 3·3 mg. %, and the results are summarised in the following table (see Figs. 6 and 7).

		Absorption band.				Absorption band.	
Fraction.	Solvent.*	λ.	log I_0/I.	Fraction.	Solvent.*	λ.	log I_0/I.
F_3	N.A.	2900	2·6	F_5	N.A.	2910	1·0
F_3	A.A.	(No band)	—	F_5	A.A.	2910	1·0
F_4	N.A.	2900	1·9	F_6	N.A.	2940	1·6
		3750	1·3	F_6	A.A.	(No band)	—
F_4	A.A.	2850	1·0				

* N.A. = Neutral alcohol; A.A. = aqueous alcohol acidified to 5N.

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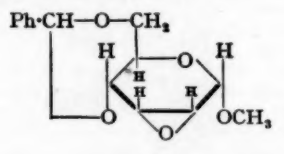
266. *Deoxy-sugars. Part II. Synthesis of 2-Deoxy-D-ribose and 3-Deoxy-D-xylose from D-Arabinose.*

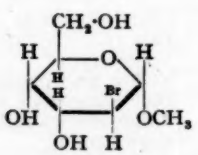
By P. W. KENT, M. STACEY, and L. F. WIGGINS.

2 : 3-*Anhydro-β-methyl*-D-*riboside* has been obtained crystalline. Its anhydro-ring has been found to open readily with hydrobromic acid to yield mainly 3-*bromo β-methyl*-D-*xyloside* together with 2-bromo β-methyl-D-arabinoside. The latter has been converted into 2-deoxy-D-ribose, but the low overall yield of this compound makes the new synthesis of little practical value. New evidence on the structure of 3-deoxyxylose is presented.

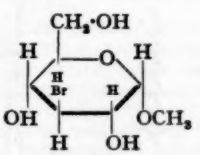
2-DEOXY-D-RIBOSE occurs as the sole identified sugar component of the deoxyribonucleic acid of cell nucleal material. It is thus a natural product of great biological importance and we are exploring various routes to its synthesis. The standard method from D-arabinal (Fischer, *Ber.*, 1914, **47**, 186; Meisenheimer and Jung, *Ber.*, 1927, **60**, 1462) as initial material does not give satisfactory yields, and the present method is concerned with the possible utilisation of 2 : 3-anhydro-sugars as the starting point. While the work was in progress, a closely similar route in the L-series was followed by Mukherjee and Todd (*J.*, 1947, 969), with essentially the same results as our own. Our approach was made possible by the work of Overend, Newth, and Wiggins (*J.*, 1947, 10), who showed that 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (I) suffers ring scission with either hydrochloric or hydrobromic acid to form a mixture of the corresponding halogeno sugars. Thus, 2-bromo (or 2-chloro) α-methylaltroside (II) and 3-bromo(or 3-chloro) α-methylglucoside (III) were isolated. In this case the former predominated, and it was noted that there was a small increase in the proportion of the glucose isomer formed as compared with the amount obtained by ring scission with alkali of the same anhydro-ring compound.



(I.)



(II.)



(III.)

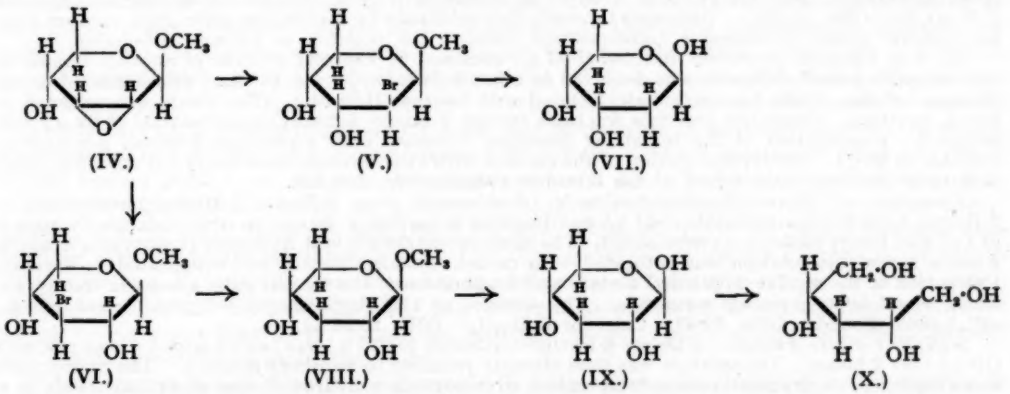
It was clear that 2 : 3-anhydromethylriboside should, by analogy with the anhydroalloside (I), undergo ring scission with hydrobromic acid to yield derivatives of 2-bromo arabinose and 3-bromo xylose. The relative amounts of these compounds, by analogy with the alloside case, should favour the production of the 2-bromo arabinose derivative. The preparation of crystalline 2 : 3-*anhydro*-β-*methyl*-D-*riboside* (IV) has now been achieved (cf. Honeyman, *J.*, 1946, 990), and its ring scission with hydrobromic acid accomplished, giving the expected two products, 2-bromo β-methyl-D-arabinoside (V) and 3-*bromo* β-*methyl*-D-*xyloside* (VI). The

relative amounts of those compounds, however, were such that it was the xylose derivative and not the arabinose derivative which was formed in predominating yield. A separation of the two products was achieved by reason of the fact that the xyloside crystallised with ease whereas the arabinoside remained liquid. Separation of these two substances was also secured by acetonisation of the mixture, whereby only the arabinoside formed an *iso*propylidene derivative, namely, 2-bromo 3 : 4-*iso*propylidene β-methyl-D-arabinoside, which remained as a liquid. An alternative and precise method of separation was by chromatographic adsorption of the mixture on an alumina column. The 2-bromo β-methylarabinoside was more readily eluted from the column than was the 3-bromo β-methylxyloside, and in this way the mixture (1·05 g.) of halogeno pentosides was resolved into the crystalline 3-bromo β-methylxyloside (0·85 g.) and the liquid 2-bromo β-methylarabinoside (0·09 g.).

The latter substance on catalytic hydrogenation over Raney nickel in the presence of calcium hydroxide gave a liquid which on mild hydrolysis with acetic acid produced 2-deoxy-D-ribose (VII), isolated as the *anilide* identical with that obtained by Deriaz, Stacey, Teece, and Wiggins (forthcoming publication). This compound gives a positive diphenylamine reaction (Dische, *Mikrochemie*, 1930, **8**, 4) identical with that given by authentic 2-deoxy-D-ribose.

This constitutes a new synthesis of 2-deoxyribose, although the relatively low yield obtained deprives the method of any preparative significance.

The designation of the crystalline bromo methylpentoside as 3-bromo β-methylxyloside (cf. Mukherjee and Todd, *loc. cit.*, for the same compound in the L-series) is shown by the



following facts: (*a*) The compound did not react with lead tetra-acetate under Hockett and McClenahan's conditions (*J. Amer. Chem. Soc.*, 1939, **61**, 1667). (*b*) Catalytic hydrogenation of the crystalline bromo methylpentoside gave a deoxymethylpentoside which failed to give Dische's test for 2-deoxypentoses. This test as developed by Deriaz, Stacey, Teece, and Wiggins (preceding paper) indicates the presence of 2-deoxypentoses only. (*c*) The deoxymethylpentoside on hydrolysis, followed by hydrogenation, afforded a crystalline deoxypentitol identified by formation of its tetrabenzoate. Both the deoxypentitol and the tetrabenzoate were optically inactive in polarized light of a range of wave-lengths in the visible spectrum. A deoxypentitol with the deoxy-group at C_3, namely, 3-deoxyxylitol, is the only deoxypentitol which shows no dissymmetry.

Hence, the bromo methylpentose is 3-bromo β-methyl-D-xyloside (VI), the hydrogenation product is 3-deoxy-β-methyl-D-xyloside (VIII), and the hydrolysis product is 3-*deoxy*-D-*xylose* (IX). 3-*Deoxy*-D-*xylitol* (X) was obtained by hydrogenation of 3-deoxy-D-xylose, and its benzoyl derivative undoubtedly was 1 : 2 : 4 : 5-*tetrabenzoyl* 3-*deoxyxylitol*. The 3-deoxy-D-xylose gave a crystalline *p*-nitrophenylhydrazone having the same melting point as that recorded by Mukherjee and Todd (*loc. cit.*) for the enantiomorph.

Experimental.

2-*Toluene*-p-*sulphonyl* β-*Methyl*-D-*arabinoside*.—The 2-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene β-methyl-D-arabinoside described by Jones, Kent, and Stacey (*J.*, 1947, 1341) (2·4 g.) was heated at 100° for 3 hours with N-acetic acid (23 c.c.). The solution was then evaporated to dryness in a vacuum over potassium hydroxide. 2-*Toluene*-p-*sulphonyl* β-*methyl*-D-*arabinoside*, crystallised and recrystallised from chloroform, had m. p. 53—55°, $[\alpha]_D^{19°}$ −177·4° in methanol (*c*, 3·4), $[\alpha]_D$ −111·1° in $CHCl_3$ (*c*, 0·2); yield 1·9 g. (Found: C, 48·8; H, 5·7. $C_{13}H_{18}O_7S$ requires C, 49·0; H, 5·7%). Honeyman (*loc. cit.*) described the enantiomorph as having m. p. 48—49°, $[\alpha]_D$ +110·9° in chloroform.

2 : 3-*Anhydro*-β-*methyl*-D-*riboside*.—To the foregoing compound (2·8 g.), dissolved in dry chloroform (10 c.c.) at 0°, was added a solution of sodium (0·2 g.) in dry methyl alcohol. After being kept for 12 hours at room temperature, the solution was diluted with chloroform (50 c.c.) and shaken with water (100 c.c.). The aqueous solution was neutralised with dilute sulphuric acid (litmus) and evaporated to dryness. The residue was extracted repeatedly with hot ethyl acetate, and the extract evaporated to dryness. The product distilled at 110° (bath temp.)/0·05 mm., and completely crystallised on cooling. The *anhydro*-compound, recrystallised from ether–ligroin, had m. p. 46°; yield 0·75 g., $[\alpha]_D^{23°}$ −35·8° in chloroform (*c*, 0·6) (Found: C, 49·0; H, 6·80; OMe, 21·3. $C_6H_{10}O_4$ requires C, 49·4; H, 6·85; OMe, 21·4%).

Ring Scission of 2 : 3-*Anhydro*-β-*methyl*-D-*riboside with Hydrobromic Acid*.—2 : 3-Anhydro-β-methyl-D-riboside (1·2 g.) was dissolved in acetone (160 c.c.) to which had been added 3·78N-hydrobromic acid (5·8 c.c.). The mixture was heated under reflux for 5 hours and then neutralised with lead carbonate. The solution was evaporated to a small bulk, diluted with water (100 c.c.), and extracted with ether in order to remove coloured impurities. The aqueous solution was evaporated to dryness, and the residue extracted with hot ethyl acetate. The product consisted of a mixture of 2-bromo β-methyl-D-arabinoside and 3-bromo β-methyl-D-xyloside.

Separation of products. (*A*) The foregoing product partly crystallised and some 3-*bromo* β-*methylxyloside* (0·9 g.) separated; m. p. 101—102°, $[\alpha]_D^{18°}$ −16·4° in methyl alcohol (*c*, 0·4) (Found: C, 31·5; H, 4·80; Br, 34·9. $C_6H_{11}O_4Br$ requires C, 31·7; H, 4·83; Br, 35·2%). This substance showed no reaction when treated with lead tetra-acetate under Hockett and McClenahan's conditions (*loc. cit.*). The residual syrup was dissolved in dry acetone (100 c.c.) containing concentrated sulphuric acid (0·3 c.c.). After being shaken for 12 hours, the solution was neutralized with anhydrous sodium carbonate, filtered, and evaporated to dryness. The product contained 3-bromo β-methyl-D-xyloside and 2-bromo 3 : 4-*iso*propylidene β-methyl-D-arabinoside. The former compound crystallised and was removed by treatment with ethyl acetate–ligroin, and the residual liquid was mainly the latter compound; $n_D^{17°}$ 1·4517, $[\alpha]_D^{17°}$ −47·1° in methanol (*c*, 0·3) (Found: OMe, 12·0. Calc. for $C_9H_{15}O_4Br$: OMe, 11·6%). Attempts to purify this substance by distillation under high vacuum were unsuccessful owing to extensive decomposition (even in the presence of barium carbonate).

(*B*) The halogeno pentoside mixture (1·05 g.) obtained by the ring scission of another sample of 2 : 3-anhydro-β-methylriboside was dissolved in ethanol–benzene (1 : 1; 100 c.c.) and adsorbed on an alumina column, which was immediately eluted with benzene (150 c.c.). The eluate was collected in 15-c.c. portions. From the first two fractions syrupy 2-bromo β-methyl-D-arabinoside (0·09 g.) was obtained. Evaporation of the remaining fractions furnished only crystalline 3-bromo β-methyl-D-xyloside (0·85 g.). By further elution of the column with ethyl acetate–benzene (1 : 1) and 75% ethyl acetate in benzene, only traces of the 3-bromo xyloside were isolated.

Formation of 2-*Deoxy*-β-*methyl*-D-*riboside* (*Arabinoside*) *from* 2-*Bromo* β-*Methyl*-D-*arabinoside*.—2-Bromo β-methyl-D-arabinoside (0·17 g.) was dissolved in methanol (30 c.c.) to which calcium hydroxide (0·1 g.) and Raney nickel (1 g.) were added. The mixture was shaken with hydrogen at room temperature. After 4 hours, the solution was saturated with carbon dioxide, filtered, and evaporated to dryness. Extraction of the residue with ethyl acetate and evaporation of the solvent gave a halogen-free syrup, which was 2-deoxy-β-methyl-D-riboside. This distilled at 112° (bath temp.)/0·02 mm.; yield 0·08 g., $n_D^{24°}$ 1·4665 (Found: OMe, 20·43. Calc. for $C_6H_{12}O_4$: OMe, 20·94%).

2-*Deoxy*-D-*ribose Anilide*.—2-Deoxy-β-methyl-D-riboside (0·075 g.) was heated with 0·01N-acetic acid (10 c.c.) for 2 hours. The solution was then strongly reducing to Fehling's solution. The hydrolysate was evaporated to dryness at room temperature over potassium hydroxide and phosphoric oxide in a vacuum desiccator. The syrupy 2-deoxy-D-ribose so obtained was heated under reflux with dry ethanolic aniline (2 c.c., 2·5%) for 3 hours. On evaporation of the solvent, a solid separated which, recrystallised from ethanol (0·04 g.), had m. p. 165—166° alone or in admixture with authentic 2-*deoxy*-D-*ribose anilide* as obtained by Deriaz, Stacey, Teece, and Wiggins (unpublished work) (Found: C, 62·92; H, 7·16. $C_{11}H_{15}O_3N$ requires C, 63·17; H, 7·18%).

3-*Deoxy*-β-*methyl*-D-*xyloside*.—3-Deoxy-β-methyl-D-xyloside (0·9 g.) was hydrogenated at room temperature by shaking a methyl-alcoholic solution of it with hydrogen under 1 atm. in the presence of Raney nickel (2 g.) and potassium hydroxide (0·1 g.). The mixture was then saturated with carbon dioxide, filtered (charcoal), and evaporated to dryness under reduced pressure. The residue was extracted with hot ethyl acetate and the extract evaporated to a syrup (0·68 g.). This 3-*deoxy*-β-*methyl*-D-*xyloside* distilled at 110—112° (bath temp.)/0·01 mm., and had $n_D^{20°}$ 1·4566, $[\alpha]_D^{19°}$ −13·3° in water (*c*, 3·0) (Found: C, 48·3; H, 8·3; OMe, 20·2. $C_6H_{12}O_4$ requires C, 48·6; H, 8·1; OMe, 20·9%).

2 : 4-*Bis*-3′ : 5′-*dinitrobenzoyl* 3-*Deoxy*-β-*methyl*-D-*xyloside* (as VIII).—3-Deoxy β-methyl-D-xyloside (0·1 g.) was dissolved in dry pyridine (10 c.c.) at 0°, 3 : 5-dinitrobenzoyl chloride (0·1 g.) added, and the mixture kept for 12 hours. Thereafter the solution was poured into water and the *ester* so obtained was recrystallised from ethanol; m. p. 157—158°; yield 0·05 g. (Found: C, 44·6; H, 2·9. $C_{20}H_{16}O_{12}N_4$ requires C, 44·8; H, 2·99%).

3-*Deoxy*-D-*xylose*.—3-Deoxy-β-methyl-D-xyloside (0·6 g.) was hydrolysed by being heated at 100° with 0·05N-hydrochloric acid (20 c.c.) for 4 hours. (During this time the $[\alpha]_D$ changed from −9·3° to −2·8°.) The resulting solution was neutralised with silver carbonate, filtered (charcoal), and evaporated to dryness at 40° under reduced pressure. The product (0·57 g.) reduced Fehling's solution and had $n_D^{16°}$ 1·4610, $[\alpha]_D^{24°}$ −6·3° (*c*, 1·3) in water. Mukherjee and Todd describe the enantiomorph as having $[\alpha]_D$ +8·7°.

3-*Deoxy*-D-*xylose* p-*Nitrophenylhydrazone*.—3-Deoxy-D-xylose (0·04 g.) was dissolved in glacial acetic acid (1·5 c.c.). *p*-Nitrophenylhydrazine (0·085 g.) was added, and the mixture heated for 45 minutes at 100°. A red solid separated which recrystallised from ethyl alcohol; m. p. 253—255°, yield 0·06 g. Mukherjee and Todd (*loc. cit.*) described the enantiomorph as having m. p. 254—256°.

3-*Deoxyxylitol*.—3-Deoxy-D-xylose (0·4 g.) was dissolved in water (250 c.c.), and Raney nickel (1·5 g.) added to the solution. The mixture was hydrogenated at 100° for 10 hours at 30 atm. The catalyst was removed by filtration (charcoal), and the solution evaporated to dryness. A colourless non-reducing

syrup (0·38 g.), $n_D^{22°}$ 1·4730, was obtained. This 3-*deoxyxylitol* crystallised on keeping, and on recrystallisation from ether–ligroin had m. p. 68—69°. The optical rotation of this compound was zero (*c*, 4·1 in ethanol) when measured in sodium light, the 5461 line of the mercury spectrum, or the red line in the cadmium spectrum (Found: C, 43·8; H, 8·90. $C_5H_{12}O_4$ requires C, 44·1; H, 8·82%).

Tetrabenzoyl 3-*Deoxyxylitol*.—3-Deoxyxylitol (0·11 g.) was dissolved in dry pyridine (4·5 c.c.) at 0°, benzoyl chloride (0·45 g.) was added, and the mixture kept for 12 hours at room temperature. When the solution was poured into ice-water (60 c.c.), the solid *tetrabenzoyl* derivative separated; this, recrystallised from ethanol, had m. p. 104—105°, $[\alpha]_D$ ±0° (for the above three lines) (Found: C, 70·9; H, 5·0. $C_{33}H_{28}O_8$ requires C, 71·5; H, 5·07%).

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267. *Deoxy-sugars. Part III. Methanesulphonyl Derivatives of* D-*Arabinose.*

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Attempts have been made to effect the exchange reaction between various 2-methanesulphonyl derivatives of D-arabinose and sodium iodide. In no case, however, was this achieved. Numerous new methanesulphonyl derivatives of the pentose are described.

THE importance of the deoxypentose of thymus nucleic acid, 2-deoxy-D-ribose, has prompted us to explore many possible methods of its preparation. One such possibility is through the reduction of a 2-halogeno arabinoside. This has been accomplished in the case of 2-bromo β-methylarabinoside, obtained by the ring scission of 2 : 3-anhydro-β-methyl-D-riboside (see preceding paper). Now it is known that, in certain cases, methanesulphonyl residues attached to a secondary carbon atom of a sugar molecule may be replaced by an iodine atom by the simple expedient of heating the methanesulphonate with sodium iodide in acetone or other ketones of higher boiling point; for instance, 4-methanesulphonyl 1 : 2 : 3 : 6-tetra-acetyl glucose upon treatment with sodium iodide in acetone solution afforded 4-iodo 1 : 2 : 3 : 6-tetra-acetyl glucose in good yield (Helferich and Gnüchtel, *Ber.*, 1938, **71**, 712). If such a reaction were possible with a 2-methanesulphonyl derivative of D-arabinose to yield a corresponding 2-iodo derivative, this, on reduction, would lead to the formation of 2-deoxy-D-ribose. For this reason we have studied the methanesulphonyl derivatives of D-arabinose, and many new derivatives of this type are now described. In no case, however, was it possible to effect the replacement of the 2-methanesulphonyl group by iodine.

Treatment of β-methyl-D-arabopyranoside (I) with excess of methanesulphonyl chloride in pyridine affords crystalline 2 : 3 : 4-*trimethanesulphonyl* β-*methyl*-D-*arabinoside*. Similarly, α-methyl-D-arabopyranoside gave a crystalline *trimethanesulphonyl* derivative in quantitative yield.

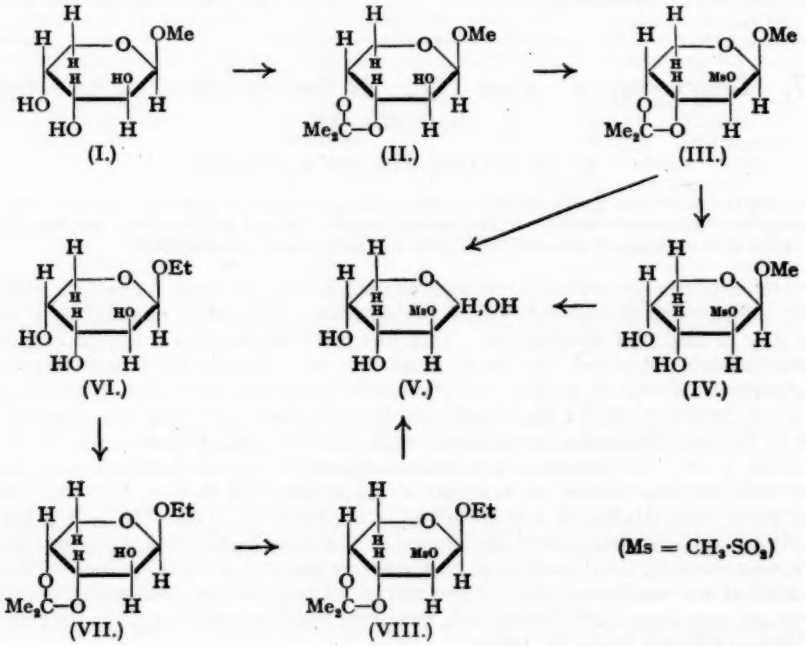
When β-methyl-D-arabinoside (I) was treated with acetone in the presence of 0·5% sulphuric acid or phosphoric oxide, syrupy 3 : 4-*iso*propylidene β-methyl-D-arabopyranoside (II) was obtained. This compound was described by Jones, Kent, and Stacey (*J.*, 1947, 1341), who also obtained the crystalline 2-toluene-*p*-sulphonyl and 2-methanesulphonyl (III) derivatives. An additional crystalline derivative, the 2-*acetyl* derivative is now described.

All attempts to convert the 2-methanesulphonyl derivative (III) into 2-iodo 3 : 4-*iso*propylidene β-methyl-D-arabopyranoside were unsuccessful. Jones, Kent, and Stacey (*loc. cit.*) have already reported that this compound (III) was unchanged after being heated with dry acetone and dry sodium iodide in a sealed tube at 112° for 48 hours. We have now recovered the material unchanged after heating it more drastically.

Removal of the *iso*propylidene residue from 2-methanesulphonyl 3 : 4-*iso*propylidene β-methyl-D-arabopyranoside (III) was effected by heating it with methyl alcohol containing 2·0% of 5N-hydrochloric acid, and crystalline 2-*methanesulphonyl* β-*methyl*-D-*arabopyranoside* (IV) was obtained. Treatment of this with hot N-sulphuric acid resulted in elimination of the glycoside group and afforded crystalline 2-*methanesulphonyl* D-*arabinose* (V). The same compound was obtained directly from (III) by hydrolysis with N-sulphuric acid. When 2-methanesulphonyl β-methyl-D-arabopyranoside (IV) was kept with acetic anhydride in dry pyridine, it yielded crystalline 2-*methanesulphonyl* 3 : 4-*diacetyl* β-*methyl*-D-*arabinoside*. Neither 2-methanesulphonyl β-methyl-D-arabopyranoside (IV) nor its 3 : 4-diacetyl derivative gave a 2-iodo compound of β-methyl-D-arabopyranoside when treated with dry acetone and sodium iodide.

It was thought that an alteration of the glycoside grouping from methyl to ethyl might have

the effect of increasing the lability of the methanesulphonyl substituent on C_2 of the arabinoside, and facilitate its exchange with iodine. Consequently 3 : 4-iso*propylidene* β-*ethyl*-D-*arabopyranoside* (VII) was prepared, treated with methanesulphonyl chloride, and the 2-*methanesulphonyl* derivative (VIII) obtained. This was isolated only as a liquid, but on hydrolysis with 1·75N-sulphuric acid, it gave 2-methanesulphonyl D-arabinose (V), identical with that prepared from 2-methanesulphonyl β-methyl-D-arabopyranoside (IV). Treatment of (VIII) with dry acetone and sodium iodide in a sealed tube gave no 2-iodo 3 : 4-*iso*propylidene β-ethyl-D-arabopyranoside, and the starting material was recovered unchanged.



It was envisaged that a change of configuration of the glycoside group in arabinose from β to α might enhance the lability of the methanesulphonyl substituent on C_2. Consequently 2-*methanesulphonyl* 3 : 4-iso*propylidene* α-*methyl*-D-*arabopyranoside* was prepared. Nevertheless, when this was heated with dry acetone and sodium iodide, no replacement of the methanesulphonyl substituent by iodine occurred.

Removal of the *iso*propylidene residue from 2-methanesulphonyl 3 : 4-*iso*propylidene α-methyl-D-arabopyranoside was effected by heating it with methyl alcohol containing 2% of 5N-hydrochloric acid, and crystalline 2-*methanesulphonyl* α-*methyl*-D-*arabopyranoside* was obtained.

Experimental.

2 : 3 : 4-*Trimethanesulphonyl* β-*Methyl*-D-*arabinoside*.—β-Methyl-D-arabinoside (0·168 g.) was dissolved in dry pyridine (5 c.c.), and the solution cooled to 0°. Methanesulphonyl chloride (3·3 mols., 0·377 g.) was slowly added, and the mixture kept at room temperature for 48 hours. After being poured into water, the material was extracted with chloroform, and the extract washed with 0·05N-sulphuric acid, then with dilute aqueous sodium hydrogen carbonate solution, and finally with water. After being dried ($MgSO_4$), the extract was evaporated to dryness, and the syrup which remained was crystallised by trituration with ethyl alcohol. Recrystallisation from absolute ethyl alcohol gave a quantitative yield of the *trimethanesulphonyl* derivative as colourless needles, m. p. 123°, $[\alpha]_D^{15\cdot5°}$ −333·3° (*c*, 0·102 in chloroform) (Found : C, 27·2; H, 4·5; OMe, 8·0. $C_9H_{18}O_{11}S_3$ requires C, 27·1; H, 4·5; OMe, 7·8%).

2 : 3 : 4-*Trimethanesulphonyl* α-*Methyl*-D-*arabinoside*.—This was prepared by the method described above for the β-compound, and recrystallised from chloroform–pyridine in colourless needles, m. p. 186—187°, $[\alpha]_D^{16°}$ −86·95° (*c*, 0·184 in chloroform); the yield was quantitative (Found : C, 27·2; H, 4·5; OMe, 7·5%).

3 : 4-iso*Propylidene* β-*Methyl*-D-*arabinoside*.—(*a*) β-Methyl-D-arabinoside (12·34 g.) was shaken with acetone (1 l.) containing 0·5% sulphuric acid and worked up in the usual way. The product was a colourless liquid, b. p. 115° (bath temp.)/0·01 mm., $n_D^{17°}$ 1·4617, $[\alpha]_D^{18\cdot5°}$ −197·6° (*c*, 0·344 in chloroform) {Honeyman, *J.*, 1946, 990, gives b. p. 82°/0·1 mm., $[\alpha]_D^{20°}$ +199·1° (*c*, 3·3 in chloroform) for 3 : 4-*iso*-

propylidene β-methyl-L-arabinoside} (yield 14·09 g., 92%) (Found OMe, 15·2. Calc. for $C_9H_{16}O_5$: OMe, 15·2%).

(*b*) β-Methyl-D-arabinoside (24·72 g.) was suspended in dry acetone (500 c.c.), and phosphoric oxide (16·6 g.) added; the product, obtained as usual, was a colourless oil, b. p. 115—120° (bath temp.)/0·01 mm., $[\alpha]_D^{20°}$ −198·4° (*c*, 0·54 in chloroform).

2-*Acetyl* 3 : 4-iso*Propylidene* β-*Methyl*-D-*arabinoside*.—Freshly distilled acetic anhydride (0·26 g., 50% excess) was added to a solution of 3 : 4-*iso*propylidene β-methyl-D-arabopyranoside (0·366 g.) in dry pyridine (10 ml.). The solution was kept at room temperature for 3 hours and then poured into water. It was then neutralised with sodium hydrogen carbonate and extracted with chloroform. The extract was dried ($MgSO_4$), and the solvent removed by evaporation. The syrupy *acetyl* derivative, crystallised on trituration with acetone–water and recrystallised from hot water, had m. p. 76·5—77·5°, $[\alpha]_D^{16°}$ −125° (*c*, 0·416 in water) (Honeyman, *loc. cit.*, quotes $[\alpha]_D^{16°}$ +123·6° in water for the L-isomer) (Found: C, 53·0; H, 7·1; OMe, 12·4. $C_{11}H_{18}O_6$ requires C, 53·6; H, 7·3; OMe, 12·6%).

Attempts to prepare 2-*Iodo* 3 : 4-iso*Propylidene* β-*Methyl*-D-*arabinoside*.—(*a*) 2-Methanesulphonyl 3 : 4-*iso*propylidene β-methyl-D-arabinoside (0·133 g.) {m. p. 136·5—137·5°, $[\alpha]_D^{24°}$ −333° in chloroform (*c*, 0·045)}, obtained according to Jones, Kent, and Stacey (*loc. cit.*), was dissolved in dry acetone (25 ml.) containing dry sodium iodide (1·1 mols., 0·079 g.), and the solution was heated in a sealed tube at 125° for 5 hours. No sodium methanesulphonate separated. After cooling, the solution was evaporated to dryness and the solid residue was leached with water. The solid then remaining was collected (0·10 g.) and had m. p., alone or in admixture with the starting material, 137°.

(*b*) The above experiment was repeated, except that the time of heating was extended to 12 hours and the temperature increased to 200°, but the starting material was recovered unchanged.

2-*Methanesulphonyl* β-*Methyl*-D-*arabopyranoside*.—2-Methanesulphonyl 3 : 4-*iso*propylidene β-methyl-D-arabopyranoside (1·87 g.) was dissolved in methyl alcohol (111 c.c.) containing 5N-hydrochloric acid (2·27 c.c.), and the solution boiled for 6 hours. After being neutralised with silver carbonate, the solution was filtered, and the filtrate evaporated to dryness. The syrupy residue was extracted with chloroform. After being dried ($MgSO_4$), the extract was evaporated to a syrup, which crystallised when triturated with ethyl alcohol and water. The solid *methanesulphonyl* derivative, recrystallised from ethyl alcohol–water, formed colourless cubes (0·86 g., 54%), m. p. 69—70°, $[\alpha]_D^{17·5°}$ −161·3° (*c*, 0·310 in chloroform) (Found: C, 32·35; H, 6·3; OMe, 13·0. $C_7H_{14}O_7S,H_2O$ requires C, 32·3; H, 6·2; OMe, 11·9%).

2-*Methanesulphonyl* 3 : 4-*Diacetyl* β-*Methyl*-D-*arabinoside*.—2-Methanesulphonyl β-methyl-D-arabinoside (0·18 g.) was dissolved in dry pyridine (5 c.c.) and freshly distilled acetic anhydride (0·432 g., 50% excess) was added to the solution. The mixture was kept at room temperature for 12 hours and then poured into water. After being neutralised with sodium hydrogen carbonate, the solution was extracted with chloroform. The extract was dried ($CaCl_2$) and then evaporated to dryness. A pale yellow syrup remained which crystallised when triturated with ethyl alcohol. Recrystallisation from ethyl alcohol–water (charcoal) gave the *diacetyl* derivative in colourless cubes, m. p. 103—104°, $[\alpha]_D^{21·5°}$ −312·5° (*c*, 0·048 in chloroform); yield 0·06 g. (Found: C, 40·5; H, 5·6. $C_{11}H_{18}O_8S$ requires C, 40·4; H, 5·6%).

Attempt to prepare 2-*Iodo* β-*Methyl*-D-*arabinoside*.—2-Methanesulphonyl β-methyl-D-arabinoside (0·10 g.) was dissolved in dry acetone (10 ml.) and dry sodium iodide (1·1 mols., 0·068 g.) was added. The mixture was heated at 110° for 5 hours in a sealed tube. After cooling and filtration, the solution was evaporated to dryness, and the residue was extracted with chloroform. Evaporation of the solution gave a syrup which completely crystallised. Recrystallisation from ethyl alcohol gave colourless needles, m. p. alone or in admixture with 6-methanesulphonyl β-methyl-D-arabinoside, 69°; yield of recovered material, 0·085 g.

Attempt to prepare 2-*Iodo* 3 : 4-*Diacetyl* β-*Methyl*-D-*arabinoside*.—2-Methanesulphonyl 3 : 4-diacetyl β-methyl-D-arabinoside (0·50 g.) was dissolved in dry acetone (15 ml.), dry sodium iodide (1·1 mols., 0·23 g.) added, and the mixture heated at 110° for 5 hours in a sealed tube. After cooling, the solution was filtered and then evaporated to dryness. The residue was extracted with chloroform and evaporation of the solution gave a syrup which crystallised on standing. Recrystallised from alcohol–water, it had m. p. 103° alone or in admixture with the starting material; yield 0·42 g.

2-*Methanesulphonyl* D-*Arabinose*.—(*a*) 2-Methanesulphonyl 3 : 4-*iso*propylidene β-methyl-D-arabinoside (1·2 g.) was heated under reflux with N-sulphuric acid (40 c.c.) for 4 hours. The solution was neutralised with barium carbonate, and then filtered through a carbon pad. The filtrate was evaporated to dryness under diminished pressure, and the residue extracted with alcohol. The extract was filtered and evaporated to a colourless syrup which crystallised on trituration with ethyl alcohol. After recrystallisation from ethyl alcohol–water, colourless plates of 2-*methanesulphonyl* D-*arabinose* were obtained; m. p. 65—66°, $[\alpha]_D^{17°}$ −187·6° changing to −203·7° after 12 minutes (*c*, 0·373 in 5 parts chloroform and 1 part ethyl alcohol). The solid (yield 0·3 g.) reduced Fehling's solution in the cold (Found: C, 32·1; H, 6·2; S, 11·4. $C_6H_{12}O_7S,0·5C_2H_6O,0·5H_2O$ requires C, 32·3; H, 6·1; S, 12·2%).

(*b*) 2-Methanesulphonyl β-methyl-D-arabopyranoside (1·0 g.) was heated under reflux with N-sulphuric acid (40 c.c.) for 4 hours. The solution was neutralised with barium carbonate, and then filtered through a carbon pad. 2-Methanesulphonyl D-arabinose (0·4 g., 42·5%) was isolated as described above; m. p. 65—66°.

β-*Ethyl*-D-*arabopyranoside*.—Dry D-arabinose (13·0 g.) was heated under reflux for 7 hours with absolute ethyl alcohol (300 c.c.) containing 1% of hydrogen chloride. After cooling, the solution was neutralised with silver carbonate and filtered. The filtrate was evaporated to dryness, and after trituration with ethyl alcohol, the residue crystallised. Recrystallisation from ethyl alcohol yielded the *arabopyranoside* as shining white plates (3·0 g., 19·5%), m. p. 134·5—135·5°, $[\alpha]_D^{23°}$ −251·9° (*c*, 1·3 in water) (Found: OEt, 25·4. $C_7H_{14}O_5$ requires OEt, 25·2%). Helferich and Appel (*Z. physiol. Chem.*, 1932, **205**, 20) give m. p. 136—137°, $[\alpha]_D$ +233·5°, for β-ethyl-L-arabinoside.

3 : 4-iso*Propylidene* β-*Ethyl*-D-*arabinoside*.—β-Ethyl-D-arabopyranoside (1·76 g.) was shaken with acetone (350 c.c.) containing 0·5% of sulphuric acid until complete solution was effected. The solution was neutralised with potassium carbonate and then filtered. The filtrate was evaporated to dryness in

the presence of potassium carbonate, and the residue extracted with ether. Evaporation of the solvent yielded a mixture of syrup and solid. The solid was separated and recrystallised from acetone, forming colourless plates of 3 : 4-iso*propylidene* β-*ethyl*-D-*arabinoside*, m. p. 89—91°, $[\alpha]_D^{23.5°}$ −188·1° (*c*, 0·404 in chloroform) (Found: C, 54·5; H, 8·3; OEt, 20·2. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3; OEt, 20·6%). The syrupy portion distilled as a colourless oil, b. p. 110—120°/0·005 mm. (0·225 g.), which crystallised on cooling. It recrystallised from acetone in long needles, which were extremely hygroscopic; m. p. *ca.* 40°, $[\alpha]_D^{21.5°}$ −128° (*c*, 0·25 in chloroform) (Found: C, 55·7; H, 8·2; OEt, 10·5%). This substance has not yet been identified.

2-*Methanesulphonyl* 3 : 4-iso*Propylidene* β-*Ethyl*-D-*arabinoside*.—3 : 4-*iso*Propylidene β-ethyl-D-arabinoside (0·064 g.) was dissolved in dry pyridine (5 c.c.), and methanesulphonyl chloride (50% excess) was added to the cooled solution. After being kept at room temperature for one day, the mixture was poured into water and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to a syrup, which could not be induced to crystallize; $[\alpha]_D^{22°}$ −172·6° (*c*, 0·464 in chloroform) (Found: OEt, 15·0. $C_{11}H_{20}O_7S$ requires OEt, 15·2%).

Attempt to prepare 2-*Iodo* 3 : 4-iso*Propylidene* β-*Ethyl*-D-*arabinoside*.—The foregoing syrupy 2-*methanesulphonyl* 3 : 4-iso*propylidene* β-*ethyl*-D-*arabinoside* (0·133 g.) and dry sodium iodide (1·1 mols.) were dissolved in dry acetone (25 ml.) and the solution was heated at 125° for 12 hours. After being cooled, the solution was evaporated to dryness, and the residue leached with water and then extracted with chloroform. The extract was dried ($MgSO_4$) and then evaporated. A syrup remained which had $[\alpha]_D^{24°}$ −174·3° (*c*, 0·450 in chloroform). It contained sulphur, but no halogen, and was unchanged material.

3 : 4-iso*Propylidene* α-*Methyl*-D-*arabinoside*.—α-Methyl-D-arabinoside (13·40 g.) was dissolved in acetone (700 c.c.) to which concentrated sulphuric acid (3·5 ml.) was added, and the mixture shaken overnight and then filtered. The filtrate was neutralised with anhydrous potassium carbonate and filtered. This filtrate was evaporated to dryness in the presence of potassium carbonate and the residue was extracted with ether. On removal of the ether, an oil remained, which distilled in two distinct fractions, A and B. Fraction A was a colourless oil, b. p. 125° (bath temp.)/0·01 mm. (5·35 g.), $[\alpha]_D^{22°}$ −27·8° (*c*, 1·798 in water), $n_D^{19.5°}$ 1·4543, and was 3 : 4-*iso*propylidene α-methyl-D-arabincside (Found: OMe, 14·7. Calc. for $C_9H_{16}O_5$: OMe, 15·2%). Fraction B was a colourless syrup, b. p. 145—150° (bath temp.)/0·01 mm., which crystallised; recrystallised from light petroleum (b. p. 60—80°), it formed clusters of large colourless plates (1·0 g.), m. p. 60—62°, $[\alpha]_D^{21.5°}$ −55·5° (*c*, 0·576 in water) (Found: C, 51·2; H, 7·9%). This substance has not yet been identified.

2-*Methanesulphonyl* 3 : 4-iso*Propylidene* α-*Methyl*-D-*arabinoside*.—3 : 4-*iso*Propylidene α-methyl-D-arabinoside (1·835 g.) was dissolved in dry pyridine (15 c.c.), and the solution cooled to 0°. Methanesulphonyl chloride (50% excess, 1·1 g.), also dissolved in dry pyridine (10 ml.), was added at 0°, and the mixture kept at room temperature for 48 hours. After being poured into water, the aqueous solution was extracted with chloroform, and the extract washed with dilute sulphuric acid, with sodium hydrogen carbonate solution, and finally with water. It was dried ($MgSO_4$), and the solvent removed by evaporation. The syrupy product crystallised when triturated with water and recrystallised from absolute ethyl alcohol in clusters of colourless needles (0·6 g., 24%); m. p. 135° (sinters, 118—120°), $[\alpha]_D^{17.5°}$ −81·5° (*c*, 0·466 in chloroform) (Found: C, 42·6; H, 6·4; OMe, 11·3. $C_{10}H_{18}O_7S$ requires C, 42·5; H, 6·4; OMe, 10·9%).

Attempt to prepare 2-*Iodo* 3 : 4-iso*Propylidene* α-*Methyl*-D-*arabinoside*.—The foregoing 2-*methanesulphonyl* 3 : 4-iso*propylidene* α-*methyl*-D-*arabopyranoside* (0·40 g.) and dry sodium iodide (1·1 mols., 0·23 g.) were dissolved in dry acetone (10 ml.) and the solution was heated at 110° for 5 hours in a sealed tube. After filtration the solution was evaporated to dryness, and then leached with water. The residue was dissolved in chloroform, and the extract was dried ($MgSO_4$). The solvent was removed by evaporation, and the residue was shown to be unchanged material (m. p. 133—134° alone or in admixture with original material).

2-*Methanesulphonyl* α-*Methyl*-D-*arabopyranoside*.—2-Methanesulphonyl 3 : 4-*iso*propylidene α-methyl-D-arabopyranoside (0·44 g.) was dissolved in methyl alcohol (26·1 c.c.) containing 5N-hydrochloric acid (0·53 c.c.). The solution was heated under reflux for 6 hours, neutralised with silver carbonate, filtered, and then evaporated to dryness. The syrupy residue, when triturated with ethyl alcohol–water, crystallised. Recrystallisation from ethyl alcohol–water gave small nodules of 2-*methanesulphonyl* α-*methyl*-D-*arabopyranoside*, m. p. 176—178°, $[\alpha]_D^{19.5°}$ −150° (*c*, 0·10 in methyl alcohol) (Found: C, 34·2; H, 6·0; OMe, 13·6. $C_7H_{14}O_7S$ requires C, 34·7; H, 5·8; OMe, 12·81%).

Hydrolysis of 2-*Methanesulphonyl* 3 : 4-iso*Propylidene* β-*Ethyl*-D-*arabinoside*.—This methanesulphonyl derivative (0·50 g.) was heated under reflux for 5 hours with 1·75N-sulphuric acid (40 c.c.). The solution was neutralised with barium carbonate, filtered, and the filtrate evaporated to dryness under diminished pressure. The residue was extracted with alcohol, and the extract evaporated. The syrupy product crystallised on nucleation with 2-methanesulphonyl D-arabinose; recrystallised from ethyl alcohol–water, it had m. p. 65—66°; yield 0·15 g.

The microanalyses were carried out by Dr. W. T. Chambers. One of us (W. G. O.) thanks the British Rubber Producers' Research Association for financial assistance which enabled him to take part in this investigation.

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268. *The Condensation of Fluorene Derivatives with Acrylonitrile.*

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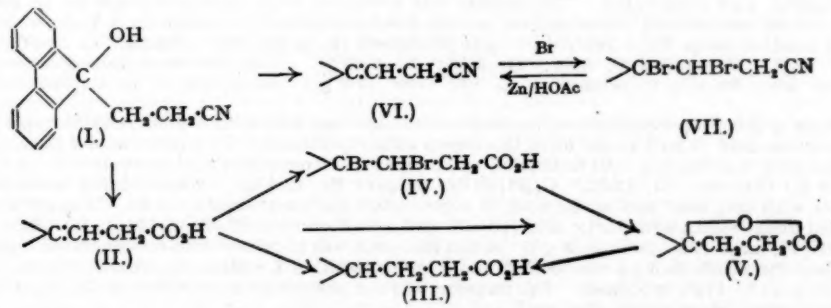
In presence of benzyltrimethylammonium hydroxide, acrylonitrile condenses with 9-phenyl- but not with 9-chloro-, 9-ethyl-, or 9-benzyl-fluorene, or ethyl 9-fluorenylglyoxylate. With 9-fluorenol it yields *β-(9-hydroxy-9-fluorenyl)propionitrile*, the reaction products of which have been studied. Among these is *β-9-fluorenylidenepropionic acid*, which is reduced to β-9-fluorenylpropionic acid from which fluoranthene is synthesised. Cinnamonitrile condenses with fluorene to yield *β-phenyl-β-9-fluorenylpropionitrile*.

In an attempt to insert a single propionic acid residue at the 9-position of the fluorene molecule the action of acrylonitrile on various fluorene derivatives in the presence of benzyltrimethylammonium hydroxide was investigated (cf. Bruson, *J. Amer. Chem. Soc.*, 1942, **64**, 2457, etc.). The failures are recorded above, but 9-phenylfluorene gave β-(9-*phenyl*-9-*fluorenyl*)*propionitrile*; hydrolysis to the *acid* and cyclisation of the acid chloride gave a product which is probably 4-*keto*-1-*phenyl*-1 : 2 : 3 : 4-*tetrahydrofluoranthene*, though formation of a spiran by ring-closure on the phenyl ring is not excluded.

9-Fluorenol reacted rapidly in dioxan with acrylonitrile in presence of the catalyst to form β-(9-*hydroxy*-9-*fluorenyl*)*propionitrile* (I). This is somewhat unexpected in view of the findings of Bruson and Riener (*J. Amer. Chem. Soc.*, 1943, **65**, 24) that acrylonitrile with alcohols forms cyanoethyl ethers. The nitrile was hydrolysed by sodium hydroxide to β-9-*fluorenylidene-*



propionic acid (II), the constitution of which follows from its preparation, catalytic reduction to β-9-fluorenylpropionic acid (III), bromination to a dibromo-acid, presumably 9 : β-*dibromo*-β-9-*fluorenylpropionic acid* (IV), and conversion by sulphuric acid into the *lactone* (V) of β-(9-hydroxy-9-fluorenyl)propionic acid. The lactone was also formed by reduction of the dibromo-acid (IV) with zinc dust and glacial acetic acid, and reduction with hydriodic acid and phosphorus (cf. Rupe and Steinbeck, *Ber.*, 1911, **44**, 584) yielded β-9-fluorenylpropionic acid (III). This acid and the lactone have both been synthesised by other methods (Meyer, *Ber.*, 1913, **46**, 2579; Campbell and Fairfull, this vol. 1102). All attempts to prepare the hydroxy-acid from the lactone were unsuccessful.

The hydroxy-nitrile (I), when refluxed with hydrochloric acid gave a mixture of β-9-*fluorenylidenepropionitrile* (VI) and the lactone (V), the lactone being obtained in good yield from this unsaturated nitrile by boiling hydrochloric acid or hydrobromic and acetic acids. The nitrile with bromine yielded 9 : β-*dibromo*-β-9-*fluorenylpropionitrile* (VII), whence it was regenerated by zinc and acetic acid.

β-9-Fluorenylpropionic acid was converted by the method of von Braun and Anton (*Ber.*, 1929, **62**, 148) into 1 : 2 : 3 : 4-tetrahydrofluoranthene and thence by chloranil dehydrogenation into fluoranthene.

Cinnamonitrile condensed with fluorene in dioxan or toluene to give β-*phenyl*-β-9-*fluorenyl-propionitrile*. Hydrolysis yielded the *acid*, which underwent ring-closure with anhydrous hydrogen fluoride to give an excellent yield of 4-*keto*-2-*phenyl*-1 : 2 : 3 : 4-*tetrahydrofluoranthene*.

Experimental.

Chromatographic adsorptions were carried out on alumina (Brockmann). Analyses were by Drs. Weiler and Strauss (Oxford).

Condensation of Fluorenol with Acrylonitrile.—The method of Werner and Grob (*Ber.*, 1904, **37**, 2896) for the preparation of 9-fluorenol gave a product, m. p. 149—152°, lacking the characteristic crystalline

appearance of fluorenol when crystallised from benzene and depressing the m. p. of an authentic sample of fluorenol (Bachmann, *J. Amer. Chem. Soc.*, 1933, **55**, 770). The product is probably the molecular compound of fluorenol and fluorenepinacol obtained by Bachmann (*J. Amer. Chem. Soc.*, 1933, **55**, 1185). Fluorenol, however, was successfully prepared by the following modification. Fluorenone (20 g.) was heated under reflux in ethanol (100 ml.) and concentrated ammonia (100 ml.), and ammonia was passed into the solution. Zinc dust (35 g.) was added in 7-g. portions at 15-minute intervals, heating was continued for a further 30 minutes, and the colourless solution filtered. The filtrate yielded 12 g. of fluorenol, m. p. 150—153° (no m. p. depression with a genuine sample), and gave with water (1 l.) a further 5·5 g. which were crystallised from benzene (m. p. 149—151°).

Acrylonitrile (3 ml.) was added dropwise to a stirred solution of 9-fluorenol (6 g.) and 20% methanolic benzyltrimethylammonium hydroxide solution (1 ml.) so that the temperature was kept at 30—40°. Stirring was continued at room temperature for 3 hours, the solution poured into water (80 ml.), and the yellow oil extracted with ether. The ethereal layer was washed several times with water, dried ($CaCl_2$), and evaporated. The oil (6·6 g.) was dissolved in hot benzene, and light petroleum (b. p. 60—80°) was added. An oily layer formed which deposited crystals of *β-(9-hydroxy-9-fluorenyl)propionitrile* (1·1 g.), m. p. 105—107° (Found: C, 81·34; H, 5·79; N, 5·89. $C_{16}H_{13}ON$ requires C, 81·66; H, 5·57; N, 5·9%). In another experiment the yellow oil (20·3 g. from 18·2 g. fluorenol) was heated under reflux for 5 hours with sodium hydroxide (8 g.) in water (200 ml.); ammonia was evolved. Dilution with water (200 ml.) gave fluorenol (1·5 g.) and a filtrate which on acidification at 60° with concentrated hydrochloric acid, yielded a semi-solid. This was dried and dissolved in boiling benzene (280 ml.); light petroleum (b. p. 100—120°; 200 ml.) was then added. *β-9-Fluorenylidenepropionic acid* (9·1 g.) separated in colourless elongated prisms, m. p. 136—137° (after further crystallisation from benzene) (Found: C, 80·81; H, 4·85. $C_{16}H_{12}O_2$ requires C, 81·4; H, 5·1%). From the mother-liquors a further 3·6 g., m. p. 129—132°, of the acid were obtained.

The yellow oil (5 g.) was heated under reflux with concentrated hydrochloric acid (150 ml.) and water (150 ml.) for 1½ hours, and the resulting oil extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was extracted with light petroleum (b. p. 100—120°), leaving a brown residue and depositing on cooling *β-9-fluorenylidenepropionitrile* (1·3 g.), which formed colourless needles, m. p. 100—101°, from light petroleum (b. p. 60—80°) (Found: C, 88·36; H, 5·14; N, 6·73. $C_{16}H_{11}N$ requires C, 88·4; H, 5·15; N, 6·45%). The above-mentioned brown residue crystallised from benzene in needles, m. p. 197—199° (1·9 g.), and proved to be the lactone (V) (see below).

Reactions of β-9-Fluorenylidenepropionitrile.—Bromine was added to *β*-9-fluorenylidenepropionitrile (0·5 g.) in acetic acid (3 ml.) at 50° until the brown colour persisted. 9 : *β-Dibromo-β-9-fluorenylpropionitrile* separated, was washed with methanol, and crystallised from acetic acid in needles, m. p. 126—127° (yield 0·35 g.) (Found: Br, 42·32. $C_{16}H_{11}NBr_2$ requires Br, 42·4%). When heated under reflux for 30 minutes with zinc dust and acetic acid, it regenerated the unsaturated nitrile. The nitrile (0·2 g.), when boiled under reflux with acetic acid (10 ml.) and hydrobromic acid (10 ml. 34%) for 1 hour, yielded the lactone (V), m. p. 198—200° (0·16 g.). A similar result was obtained with concentrated hydrochloric acid. When the nitrile (0·5 g.) was boiled under reflux with 10% sodium hydroxide (20 ml.), fluorene (0·14 g.), m. p. 111—113°, sublimed. The fluorene was not present as such in the nitrile, since the latter gave no sublimate when water was used.

Reactions of β-9-Fluorenylidenepropionic Acid.—Bromine (1·6 g.) was added to the acid (II) (2·4 g.) in acetic acid, and, after 3 hours, water was added. The precipitate was extracted with boiling light petroleum (b. p. 100—120°) which, when cold, yielded 9 : *β-dibromo-β-9-fluorenylpropionic acid*, which formed elongated prisms from benzene, m. p. 166—167° (Found: Br, 40·74. $C_{16}H_{12}O_2Br_2$ requires Br, 40·34%). The crude product was boiled under reflux with zinc dust (5 g.) in acetic acid (10 ml.) for 15 minutes; filtration, followed by addition of water, gave the lactone (V), m. p. 198—200° (41% yield after crystallisation from benzene), of *β*-(9-hydroxy-9-fluorenyl)propionic acid.

The acid (II) (2·4 g.) in acetic acid was reduced with hydrogen (60 lb. pressure) and an Adams platinum catalyst (0·1 g.). When there was no further fall in pressure, air was admitted and the solution shaken. A further addition of the catalyst (0·1 g.) with hydrogen completed the hydrogenation. The volume of the solution was reduced to 10 ml., whereafter water gave an oily precipitate which was extracted several times with light petroleum (b. p. 100—120°) to give *β*-9-fluorenylpropionic acid, needles (from benzene), m. p. 141—142° (lit., 144°) (Found: C, 80·28; H, 6·25. Calc. for $C_{16}H_{14}O_2$: C, 80·63; H, 5·92%). This acid was also formed by heating the lactone (V) (7·5 g.) with red phosphorus (6 g.), hydriodic acid (*d* 1·9; 25 ml.), and water (10 ml.) for 5 hours under reflux. The mixture was added to water (50 ml.) and extracted with ether. The ethereal layer was washed successively with 1% sodium carbonate, aqueous sodium hydrogen sulphite, and water. The ethereal layer was extracted with sodium carbonate (50 ml. of 60% in 10-ml. portions). Acidification gave a sticky solid, which was extracted five times with 30-ml. portions of light petroleum (b. p. 100—120°) and on cooling yielded *β*-fluorenylpropionic acid, m. p. 143—144°.

The acid (II) (8 g.) was heated under reflux with 10% sulphuric acid (150 ml.) for 2½ hours, and the mixture poured on ice–water. The *lactone* (V) separated (7·7 g.) and crystallised from benzene in needles, m. p. 200—201°, with a blue fluorescence (Found: C, 80·77; H, 5·0. $C_{16}H_{12}O_2$ requires C, 81·0; H, 5·4%).

Synthesis of Fluoranthene.—*β*-9-Fluorenylpropionic acid (4·8 g.) was converted into the acid chloride by thionyl chloride and then treated in light petroleum (b. p. 100—120°) with aluminium chloride (von Braun and Anton, *Ber.*, 1929, **62**, 148), thereby giving an oil (3·3 g.) containing 4-keto-1 : 2 : 3 : 4-tetrahydrofluoranthrene [characterised by its 2 : 4-*dinitrophenylhydrazone*, orange crystals (from acetic acid), m. p. 234—236° (Found: N, 13·7. $C_{22}H_{16}O_4N_4$ requires N, 13·96%)]. Chromatographic purification of the oil in benzene on a column, 18″ × 1″, and development with benzene–light petroleum (1 : 1) gave a bright-blue-fluorescing band which separated in the filtrate to give an oil (1·8 g.) and 0·2 g. of yellow prisms (from benzene–light petroleum), m. p. 94—97° (lit., 98°), both of which yielded the dinitrophenylhydrazone described above. On Clemmensen reduction (von Braun *et al.*, *loc. cit.*),

followed by chloranil dehydrogenation (Tobler *et al.*, *Helv. Chim. Acta*, 1941, **24**, 100E), the oil gave fluoranthene, m. p. 105—107° (0·06 g.), identified by mixed m. p. and by the picrate.

Condensation of Fluorene and Cinnamonitrile.—Cinnamamide (13 g.) was heated under reflux with thionyl chloride (20 ml.) for 1 hour, the excess of thionyl chloride removed in a vacuum, and the crude cinnamonitrile distilled (b. p. 180—185°/100 mm.), dissolved in ether, and shaken with potassium carbonate solution. Removal of the ether, followed by distillation, gave cinnamonitrile, b. p. 176°/76 mm. (yield, 7 g.; 62%).

Fluorene (5 g.) was heated on the steam-bath for 3½ hours with cinnamonitrile (4·5 g.) and 1 ml. 20% methanolic benzyltrimethylammonium hydroxide in dioxan (35 ml.), and the mixture was poured into water. The resulting solid was boiled with charcoal in ethanol, and water added to the hot filtrate until turbidity occurred. When the mixture cooled, *β-phenyl-β-9-fluorenylpropionitrile* separated; it formed prisms, m. p. 151—152° (yield 4·5 g.; 50%), from aqueous ethanol (Found: N, 4·36. $C_{22}H_{17}N$ requires N, 4·75%). The nitrile (9 g.) was boiled under reflux in ethanol (200 ml.) and water (100 ml.) containing sodium hydroxide (15 g.) for 20 hours. The solution, when cold deposited *β-phenyl-β-9-fluorenylpropionamide*, needles (from ethanol), m. p. 207—208° (yield 2·7 g.), identical with a sample prepared from the acid chloride and ammonia (Found: N, 4·33. $C_{22}H_{19}ON$ requires N, 4·51%). With concentrated hydrochloric acid the filtrate gave 6·2 g. of *β-phenyl-β-9-fluorenylpropionic acid*, m. p. 181—182° after crystallisation from aqueous ethanol (Found: C, 84·28; H, 5·93. $C_{22}H_{18}O_2$ requires C, 84·02; H, 5·9%). The *methyl* ester crystallised from benzene–light petroleum (b. p. 40—60°) (1 : 3) in needles, m. p. 81—82° (Found: C, 83·71; H, 6·4. $C_{23}H_{20}O_2$ requires C, 84·05; H, 6·14%). The acid (1·7 g.) was also obtained by hydrolysing the amide (2 g.) in ethanol (75 ml.) and water (100 ml.) with sodium hydroxide (4 g.) for 30 hours. To the acid (2·5 g.) in a platinum basin, anhydrous hydrogen fluoride (approx. 100 c.c.) was added. After 18 hours the hydrogen fluoride was evaporated, and the residue of *4-keto-2-phenyl-1 : 2 : 3 : 4-tetrahydrofluoranthene* triturated with ether and crystallised from glacial acetic acid; prisms, m. p. 162—163° (yield, 90%) (Found: C, 88·80; H, 5·36. $C_{22}H_{16}O$ requires C, 89·12; H, 5·44%).

Condensation of 9-Phenylfluorene with Acrylonitrile.—Acrylonitrile (2·5 g.) was added dropwise to a stirred solution of 9-phenylfluorene (5 g.) in dioxan (40 ml.) containing 0·5 ml. of catalyst (see above), the temperature being kept below 35°. After a further 2 hours at room temperature the mixture was poured into water, and the precipitate of *β-phenyl-β-9-fluorenylpropionitrile* crystallised from acetic acid or benzene–light petroleum; it formed elongated prisms, m. p. 148—149° (yield, 4·5 g.) (Found: N, 4·36. $C_{22}H_{17}N$ requires N, 4·73%). The nitrile (20 g.) was heated under reflux with sodium hydroxide (30 g.) in ethanol (400 ml.) and water (200 ml.) for 10 hours, and added to ice–water (1500 ml.). The solution was boiled with charcoal, filtered and on acidification yielded *β-phenyl-β-9-fluorenylpropionic acid*, plates (from aqueous ethanol), m. p. 159—160° (yield, 20 g.; 90%) (Found: C, 83·57; H, 6·04. $C_{22}H_{18}O_2$ requires C, 84·1; H, 5·7%). The *methyl* ester forms colourless needles (from ethanol), m. p. 97—98° (Found: C, 84·2; H, 6·38. $C_{23}H_{20}O_2$ requires C, 84·2; H, 6·1%). The acid (1·5 g.) was converted into the acid chloride and cyclised in light petroleum with aluminium chloride (see above). Acid was removed from the product with alkali, and the residue (0·72 g.) in benzene adsorbed on a column, 15″ × 1″, and developed with this solvent. The filtrate was collected in 75-ml. portions, one of which yielded an oily solid which after several crystallisations from benzene–light petroleum yielded *4-keto-1-phenyl-1 : 2 : 3 : 4-tetrahydrofluoranthene*, m. p. 147—149° (yield, 0·18 g.) (Found: C, 88·4; H, 5·31. $C_{22}H_{16}O$ requires C, 89·2; H, 5·4%); the *2 : 4-dinitrophenylhydrazone* formed orange needles (from acetic acid), m. p. 302—303° (Found: N, 11·7. $C_{28}H_{20}O_4N_4$ requires N, 11·8%).

9-Alkylfluorenes.—The alkylfluorenes were prepared from the 9-alkylfluorenols by reduction with hydriodic acid (*d* 1·90) in acetic acid (Wanscheidt and Moldanski, *Ber.*, 1931, **64**, 917) but, contrary to statements by these authors, we were unable thus to reduce 9-methylfluorenol, m. p. 172—173° (lit., 173°) (Found: C, 85·39; H, 6·13. Calc. for $C_{14}H_{12}O$: C, 85·63; H, 6·16%), the product isolated having a m. p. much higher than that of 9-methylfluorene. 9-Benzylfluorenol gave an 85% yield of 9-benzylfluorene, m. p. 131—133° (lit., 133°) (Found: C, 93·73; H, 6·61. Calc. for $C_{20}H_{16}$: C, 93·74; H, 6·26%).

The authors acknowledge their indebtedness to the Anglo-Iranian Oil Company for a grant, and to Dr. R. S. Gow for carrying out the hydrogen fluoride cyclisation.

UNIVERSITY OF EDINBURGH. [*Received, November 12th*, 1948.]

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269. *Chemistry of the* Coprosma *Genus. Part IV. The Non-glycosidic Anthraquinone Compounds from* Coprosma lucida.

By LINDSAY H. BRIGGS and G. A. NICHOLLS.

The bark of *Coprosma lucida* contains a large quantity of anthraquinone compounds present in the free state or as glycosides. This paper describes the non-glycosidic compounds, eight of which have been obtained by chromatographic absorption, *viz.*, anthragallol, its 2-methyl and 1 : 2-dimethyl ether, 1 : 6-dihydroxy-2-methylanthraquinone, rubiadin, 3-hydroxy-2-methylanthraquinone, a minute amount of an unidentified compound, and a new trihydroxy-2-methylanthraquinone, for which the name *lucidin* is proposed.

Coprosma lucida (Forster and Forster, *Char. Gen. Pl.*, 1776, 138; Oliver, "The Genus Coprosma," *Bernice P. Bishop Museum Bulletin* 132, 1935) is a robust shrub or slender tree, attaining a height of 5—6 m. and growing throughout New Zealand, to which it is endemic. It is one of the

species called " Karamu " by the Maoris, who used it for dyeing their phormium cloths shades of yellow. Aston (*New Zealand J. Sci. Tech.*, 1918, **1**, 3,264) recorded the crimson colour given by the yellow bark with alkali and the stable dyes with chrome or alumina mordants.

Preliminary investigations on the bark indicated the presence of anthraquinone compounds both in the free state and combined as water-soluble glycosides. This paper describes the former compounds; the glycosides will be described later.

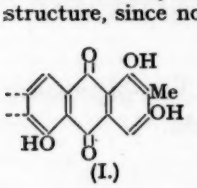
The free anthraquinone compounds could be obtained by either of two methods. In the first, the dried bark was extracted to completion with benzene, from which a compound (now named *lucidin*) separated on cooling, leaving the remaining free anthraquinone compounds in solution. The residual bark was then extracted with water to remove the glycosides, dried, and extracted to completion with acetone, from which compound *A* separated on cooling. The traces of free anthraquinone in the residual acetone solution were then combined with those extracted with benzene.

In the second method, the dried bark was extracted with acetone. Most of the free anthraquinones remained in solution but the glycosides, lucidin, and traces of the free compounds separated out on cooling. The glycosides were separated by solution in water, and the residual water-insoluble compounds added to the main quantity of the free anthraquinone compounds.

The material from both methods was taken up in dry acetone, chromatographed on calcined magnesia, and eluted with acetone until the eluate was colourless. The eluate was concentrated, and chromatographed on a fresh column. This process was repeated until all the material was adsorbed in a series of columns equivalent to one long fully developed column. The material recovered from the individual bands was rechromatographed on smaller columns, and the process repeated, on still smaller columns if necessary, until a series of compounds was obtained each giving a single band on the chromatogram.

Lucidin does not appear on the chromatogram. Its outstanding characteristic is its relative insolubility in nearly all normal organic solvents, but it could be purified by crystallisation from dioxan. Its composition, $C_{15}H_{10}O_5$, its properties, and those of its derivatives indicated a new compound. It has also been isolated from *C. acerosa* (succeeding paper).

Lucidin has colour reactions typical of a hydroxyanthraquinone, its solubility in sodium carbonate solution and positive colour reaction with ferric chloride solution indicating, respectively, at least one free β- and α-hydroxyl group. It forms a *triacetate*, a *tribenzoate*, and a *trimethyl ether* with methyl sulphate and potassium carbonate, indicating three phenolic groups. The preparation of a *monomethyl ether*, which is insoluble in sodium carbonate solution and may be characterised as its *diacetate*, indicates the presence of one β- and two α-hydroxyl groups, the former being much more readily methylated (cf. Perkin, *J.*, 1899, **75**, 433). A *C*-methyl determination, made difficult through the insolubility of lucidin in the oxidising mixture, indicates the presence of one such group, present in the β-position as shown by the isolation of 2-methylanthraquinone on distillation of lucidin with zinc. The lack of dyeing properties (on wool mordanted with dichromate or chromium, ferrous or copper sulphate) indicates that the β-hydroxy-group is not adjacent to either of the α-hydroxy-groups, and the lack of fluorescence of a glacial acetic acid solution of lucidin shows that the α-hydroxy-groups do not have a 1 : 4-relationship (cf. Raistrick, Robinson, and Todd, *Biochem. J.*, 1934, **28**, 599). There is a strong similarity in the absorption spectra of lucidin with xanthopurpurin and especially with rubiadin, indicating a 1 : 3 : 5-trihydroxy- or, less probably on phytochemical grounds, a 1 : 3 : 8-trihydroxy-structure, since no 1 : 8-compounds have yet been isolated from members of the *Rubiaceae*. The structure (I) is suggested for lucidin, but structures with the methyl group in positions 6 or 7 are not excluded.



(I.)

The compounds separated by chromatography were then examined in turn and, with one exception, have been identified with known compounds.

The first purple band was firmly attached to the magnesia and could not be removed by elution. The second band could readily be displaced from the first band, however, by the addition of a drop or two of acetic acid to the acetone used for development, a technique for which we are indebted to Mr. B. R. Thomas. The material from the first band proved to be a mixture, which was first purified by sublimation in a high vacuum and then separated by fractional crystallisation from benzene into two compounds. One, which was sparingly soluble in benzene, was identified as anthragallol by mixed m. p., colour reactions, and the preparation of the known triacetate. This is the first record of its natural occurrence, although its methyl ethers have been isolated. Perhaps the ease of oxidation of anthragallol in alkaline media has precluded its detection in the older methods of investigation where chromatography was not used.

The other compound, more readily soluble in benzene, was isolated as a red amorphous powder, m. p. 150—155°, giving violet and deep wine-red colorations in alkali and concentrated sulphuric acid respectively. Owing to the small amount of material isolated (17 mg.) and our inability to crystallise it, a detailed examination could not be made.

From the second reddish-brown band another compound was isolated; this was identified with anthragallol 2-methyl ether (Kubota and Perkin, *J.*, 1925, **127**, 1894) by its composition, m. p., and the preparation of the known diacetate and anthragallol trimethyl ether, the m. p. of the latter being undepressed by an authentic specimen. This is the first record of its natural occurrence, but it has since been isolated from *C. acerosa* (succeeding paper).

From the third pink-red band, a compound was isolated which, in our opinion, is identical with 1 : 6-dihydroxy-2-methylanthraquinone. Only 14 mg. were isolated and the compound was difficult to purify. Despite low m. p.s, 233—234° and 203—205°, compared with 289° and 215° of the known compound and its diacetate respectively, the mixed m. p. of the acetates was 210—213°, and the colour reactions, the colour of its band and its position on the chromatogram between anthragallol 2-methyl ether and anthragallol 1 : 2-dimethyl ether in both *C. lucida* (see below) and *C. acerosa* (succeeding paper), leave little doubt, in our opinion, as to its identity. Mitter (*J. Indian Chem. Soc.*, 1928, **5**, 769) considers that 1 : 6-dihydroxy-2-methylanthraquinone is identical with a compound, m. p. 282°, occurring in *Morinda umbellata* (Perkin and Hummel, *J.*, 1894, **65**, 854) and with soranjidiol, m. p. 276°, from *M. citrifolia* (Oesterle and Tisza, *Arch. Pharm.*, 1908, **246**, 158). It has been synthesised by Simonsen and Rau (*J.*, 1921, **119**, 1339) and by Bhattacharya and Simonsen (*J. Indian Inst. Sci.*, 1927, **10**, *A*, 6).

From the fourth orange band a compound has been isolated and identified with anthragallol 1 : 2-dimethyl ether by its m. p., colour reactions, and the preparation of the known acetate and of anthragallol trimethyl ether. Anthragallol 1 : 2-dimethyl ether has been isolated from the root-bark of *Oldenlandia umbellata* or chay root (Perkin and Hummel, *J.*, 1893, **63**, 1157; 1895, **67**, 817) and from *C. acerosa* (succeeding paper). It has been synthesised by Perkin and Story (*J.*, 1929, 1399).

From the fifth red band has been isolated rubiadin, identified by mixed m. p., colour reactions, and the preparation and identification of the known diacetate and dimethyl ether. This is the first recorded natural occurrence of rubiadin, but it has since been found as a trace impurity in rubiadin 1-methyl ether isolated from either *C. australis* or *C. areolata* (future communication). Its 3-glucoside, however, occurs in the root bark of *Rubra tinctorium L.* (madder) (Schunck and Marchlewski, *J.*, 1893, **63**, 969; Schunck, *Phil. Trans.*, 1853, **143**, 67), and its 3-primveroside in the root of *Galium verum* (Hill and Richter, *J.*, 1936, 1714) and *G. mollugo* (*idem*, *Proc. Roy. Soc.*, 1936—1937, **121**, *B*, 547). Rubiadin has been synthesised by Mitter and Biswas (*J. Indian Chem. Soc.*, 1930, **7**, 839), by Jones and Robertson (*J.*, 1930, 1699), and by Kusaka (*J. Pharm. Soc. Japan*, 1935, **55**, 110).

The last pink band afforded 3-hydroxy-2-methylanthraquinone, identified by m. p., colour reactions, the m. p. and composition of its acetate, and the preparation of its methyl ether. This is the first record of this compound in Nature but it has been synthesised by Baeyer and Fraude (*Annalen*, 1880, **202**, 163) and by more recent workers, including Waldmann and Sellner (*J. pr. Chem.*, 1938, **150**, 147) who record the highest m. p., 302°, compared with 260—262° of Baeyer and Fraude. Both this compound and its acetyl derivative were identical (mixed m. p.s) with specimens kindly supplied by Professor Mitter.

Experimental.

The bark was collected in December and January from Titirangi and Muriwai. The fresh bark is canary-yellow in colour, *ca.* ¼ inch thick, gives a bright red colour with alkali and a green solution containing a greenish-black precipitate when warmed with dilute hydrochloric acid, the latter reaction indicative of asperuloside (forthcoming communication). The air-dried, mechanically ground bark was finally dried in a desiccator for 7—10 days.

The dried bark (162 g.) was continuously extracted with benzene (45 hours) in a Soxhlet apparatus. The same bark was dried, transferred to boiling water (800 c.c.), boiled for 20 minutes, filtered off, and washed with boiling water (200 c.c.). The aqueous extract contains the glycosides to be described in a later communication. The bark was again dried and extracted to completion with acetone (15 hours; Soxhlet). Yellow needles separated from the hot acetone extract and a further crop separated on concentration. This *lucidin* (2·2 g.) was filtered off, and the extract concentrated to *ca.* 30 c.c. and poured into water. The yellow precipitate (450 mg.) gave the same chromatogram in a test as the material from the benzene extract, to which it was then added.

The whole of the material from the benzene extract (6·2 g.), including the small amount from the acetone extract, was heated under reflux with alcohol (250 c.c.) and filtered hot. A yellow pigment was filtered off (220 mg.) which proved to be identical with lucidin from the acetone extract. On cooling and standing, the alcoholic solution deposited brown amorphous material (800 mg.) which gave no

colour with alkali and was neglected. The remaining alcoholic solution was taken to dryness, and the residue dissolved in dry acetone and chromatographed on fresh or calcined magnesia (B.P. magnesia levis), sieved before use. Alumina could not be used as even from poor grades the colouring matters could not be removed after absorption.

Lucidin.—This was purified by solution in 2% sodium hydroxide solution, filtering and reprecipitating by acidification. After repeated crystallisation from dioxan, it formed yellow needles, m. p. above 330°, giving a single band when chromatographed on magnesia from a dioxan solution (Found : C, 66·4; H, 3·9. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%). The *C*-Me value, as determined by the Kuhn–Roth method, was difficult to obtain owing to the insolubility of the material in the oxidising medium (Found : *C*-Me, 4·7. $C_{15}H_{10}O_5$ requires *C*-Me, 10·0%). A Zeisel determination likewise could not be made owing to the insoluble nature of lucidin, but other facts indicate the absence of methoxy-groups.

Absorption Spectra.—The absorption spectra of the following compounds were measured in concentrated sulphuric acid and alcoholic solution using a Beckmann model DU spectrophotometer. We are greatly indebted to Mr. T. J. Sprott for these measurements.

In H_2SO_4.		In EtOH.		In H_2SO_4.		In EtOH.		In H_2SO_4.		In EtOH.	
log ε.	$\lambda_{max.}$, A.	log ε.	$\lambda_{max.}$, A.	log ε.	$\lambda_{max.}$, A.	log ε.	$\lambda_{max.}$, A.	log ε.	$\lambda_{max.}$, A.	log ε.	$\lambda_{max.}$, A.
Lucidin.				1 : 3-Dihydroxyanthraquinone.				Rubiadin.			
4·18	2460 *	4·47	2460	3·90	2650	4·43	2460	4·12	2460	4·39	2460
4·35	2890	4·46	2800	3·99	2870	4·36	2840	4·48	2890	4·52	2800
3·97	3200 *	—	—	3·71	3200	—	—	3·96	3200 *	—	—
4·07	4600	3·88	4150	3·73	4600	3·79	4150	4·02	4600	3·87	4150

* Points of inflexion.

Lucidin is soluble in 10% sodium hydroxide, sodium carbonate, and ammonium hydroxide solutions, giving red solutions, soluble in concentrated sulphuric acid with an orange-red colour, and gives a brown coloration with ferric chloride solution.

Triacetate. Lucidin (100 mg.) was heated with acetic anhydride (1·5 c.c.) and pyridine (2 c.c.) for ½ hour. After the mixture had been poured on cracked ice (100 g.), the *triacetate* (135 mg.) crystallised from alcohol in pale yellow needles of constant m. p. 175—178° (Found : C, 63·8; H, 4·6. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·2%).

Tribenzoate. Lucidin (100 mg.) was heated with benzoyl chloride (1 c.c.) and pyridine (4 c.c.) for an hour and transferred to ice-cold water (150 c.c.). After standing, the solution was decanted from the oily red mass which separated, and the latter was triturated with 5% sodium hydrogen carbonate solution (100 c.c.), filtered off, and washed with the minimum of alcohol. The almost colourless *tribenzoate* then crystallised from glacial acetic acid in pale yellow prisms of constant m. p. 204—205° (Found : C, 72·7; H, 4·2. $C_{36}H_{22}O_8,H_2O$ requires C, 72·0; H, 4·0%).

Monomethyl ether. A solution of lucidin (1 g.) in acetone (75 c.c.) was heated with methyl sulphate (3 c.c.) and anhydrous potassium carbonate (10 g.) for ½ hour. The carbonate was filtered off, washed with acetone, shaken, and washed with water until the filtrate was colourless. The red insoluble potassium salt afforded the *monomethyl ether* on treatment with dilute hydrochloric acid, crystallising from alcohol in orange-yellow needles of constant m. p. 184·5—185° (Found : C, 66·0; H, 4·5; OMe, 10·8. $C_{16}H_{12}O_5,\frac{1}{2}H_2O$ requires C, 65·5; H, 4·5; OMe, 10·6%). The monomethyl ether forms a red insoluble sodium salt with sodium hydroxide solution but is insoluble without change of colour in sodium carbonate solution. Ferric chloride gives a brown coloration. The *diacetate* was formed from the monomethyl ether (150 mg.) by acetylation with acetic anhydride (1 c.c.) and concentrated sulphuric acid (1 drop). The product (180 mg.) from pouring the mixture into ice-cold water (50 c.c.), after repeated crystallisation from acetic anhydride, formed yellow plates, m. p. 173—174·5° (Found : C, 64·9; H, 4·2; Ac, 23·1. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4; 2Ac, 23·4%).

Trimethyl ether. The acetone filtrate and acetone washings from the preparation of the monomethyl ether were concentrated to a small volume and poured into water. The pale yellow precipitate (300 mg.) gave no colour change with alkali and crystallised from alcohol in pale yellow needles of constant m. p. 173° (Found : C, 68·2, H, 5·05; OMe, 22·1, 22·5. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2; 3OMe, 29·8%). By increasing the reaction time in the above preparation to 24 hours, lucidin could be completely converted into the fully methylated derivative.

Distillation of Lucidin with Zinc Dust.—A mixture of lucidin (200 mg.) and zinc dust (4 g.) was heated in a hard-glass tube in a stream of hydrogen, with a further quantity of zinc dust (1 g.) beyond the mixture. The pure zinc dust was kept at a dull red heat while the mixture was gradually raised to the same temperature. The sublimate (10 mg.) from the cool part of the tube, together with that from a second distillation, crystallised from alcohol in almost colourless leaflets, and after three crystallisations had m. p. 202°, and 211—213° when mixed with pure 2-methylanthracene, m. p. 216°, kindly presented by Dr. B. Siegfried, Zofingen.

Chromatographic Separation of the Remaining Colouring Matters.—The whole solution of the remaining free anthraquinone compounds in acetone was poured over one absorption column (5 × 12 cm.) and eluted until the eluate was almost colourless. The eluate was concentrated to 120—150 c.c., and the process repeated on fresh columns until all the coloured compounds were absorbed and developed in a series of columns.

The final colourless eluate, on concentration to *ca.* 5 c.c., deposited colourless needles (30 mg.) which, after recrystallisation from acetone, had m. p. 210—220°. The compound did not dissolve in 10% sodium hydroxide solution or in concentrated sulphuric acid and was not further examined.

In the case of the first section of the series this alone was further eluted with acetone containing sufficient glacial acetic acid (2 c.c.) for the removal of the second band from the first, which remained unchanged. The columns were then extruded, cut into their bands, and decomposed with dilute hydrochloric acid. The material from the second, fourth, and fifth larger bands was purified by dissolving

in acetone and rechromatographing. The material from the smaller bands, together with that from the corresponding bands of the rechromatographs, was rechromatographed on 2·7-cm. diameter columns. The material from the final small bands was collected and chromatographed on 1·7-cm. diameter tubes, a system which separated all the components into pure chromatograms.

Identification of the Compounds from the Chromatograph Bands.

Band I (147 mg.): *Anthragallol, and an Unidentified Compound.*—The amorphous brown substance from this band was first sublimed at 110—180°/0·01 mm. The red sublimate (38 mg.) was separated into two fractions by their difference of solubility in benzene. The orange-brown, sparingly soluble portion (14 mg.) crystallised from nitrobenzene in needles, m. p. 310° undepressed by a specimen of anthragallol. This dissolved in 10% sodium hydroxide solution with a green colour, oxidising in air to a brown solution, a reaction typical of anthragallol. The acetate crystallised from glacial acetic acid as pale yellow needles, m. p. 187—189°, undepressed by anthragallol triacetate.

From the benzene-soluble fraction was obtained a bright red substance (17 mg.), m. p. 150—155°, insoluble in water but readily soluble in organic solvents. This could not be purified and has not been identified.

Band II (1·6 g.): *Anthragallol 2-Methyl Ether.*—From this band an amorphous brown substance was isolated which sublimed as yellow needles below 180° and melted at 215—218°. It could not be conveniently recrystallised, so was repurified by sublimation at 160—180°/0·01 mm. and then had m. p. 218° (Found: C, 66·5; H, 3·9; OMe, 9·9. Calc. for $C_{15}H_{10}O_5$: C, 66·7; H, 3·7; OMe, 11·5%). It gave a red colour with alkali and concentrated sulphuric acid. Kubota and Perkin (*loc. cit.*) record yellow needles, m. p. 218—220°, for anthragallol 2-methyl ether with the same colour reactions. In addition, the compound is soluble in 5% sodium carbonate solution and gives a brown coloration with ferric chloride solution. The acetate, prepared by acetylation with acetic anhydride and concentrated sulphuric acid, crystallised from alcohol in long yellow rods, m. p. 145—146·5°, unchanged by further crystallisation. Kubota and Perkin (*loc. cit.*) describe their acetate as large prismatic needles, m. p. 152—154°.

Anthragallol trimethyl ether was prepared from the monomethyl ether (60 mg.) with methyl sulphate and anhydrous potassium carbonate in acetone solution. After crystallisation from acetone it had m. p. 167°, undepressed by an authentic specimen (Bock, *Monatsh.*, 1902, **23**, 100).

Band III (14 mg.): 1 : 6-*Dihydroxy-2-methylanthraquinone.*—The small quantity of pigment from this band could not be readily purified. After two attempts to crystallise it from 60% ethyl alcohol it softened on heating to 220° and commenced to sublime as yellow needles before melting at 233—234°. Its colour reactions, red with 10% sodium hydroxide solution, brown-red with concentrated sulphuric acid, brown with ferric chloride solution, and its solubility in sodium carbonate solution are the same as those of 1 : 6-dihydroxy-2-methylanthraquinone, m. p. 290°, isolated from a similar band on the chromatogram of the pigments from *C. acerosa* (succeeding paper). Simonsen and Rau (*loc. cit.*) describe this compound as brown needles, m. p. 281°, giving a red colour in alkali and sulphuric acid.

The compound (8 mg.) was acetylated by warming with acetic anhydride (0·5 c.c.) and concentrated sulphuric acid (1 drop) to 60—70° for 10 minutes. The product (6 mg.), formed by pouring the mixture into water, crystallised from alcohol in pale yellow needles, m. p. 203—205°, raised to 210—213° on admixture with the diacetate of 1 : 6-dihydroxy-2-methylanthraquinone, m. p. 214°, which Simonsen and Rau (*loc. cit.*) describe as yellow needles, m. p. 212°.

Band IV (87 mg.): *Anthragallol* 1 : 2-*Dimethyl Ether.*—The yellow pigment from this band crystallised from alcohol in rhombohedral plates of constant m. p. 233—236°. It gives an orange-red solution with alkali, is insoluble in sodium carbonate solution, and gives no colour reaction with ferric chloride solution. Perkin and Story (*loc. cit.*) describe anthragallol 1 : 2-dimethyl ether as yellow plates, m. p. 230—232°, giving a red colour with alkali. The acetate, prepared as for the previous derivative, crystallised from alcohol in long yellow needles, m. p. 177—179°. Perkin and Story describe the acetate of anthragallol 1 : 2-dimethyl ether as bright yellow needles, m. p. 177—179°. The product from methylation, carried out as before, crystallised from acetone in pale yellow needles, m. p. 169°, undepressed by a sample of anthragallol trimethyl ether.

Band V (160 mg.): *Rubiadin.*—The yellow pigment from this band crystallised from glacial acetic acid in yellow plates, m. p. 302°, undepressed by an authentic specimen of rubiadin of the same m. p. Schunck and Marchlewski (*J.*, 1893, **63**, 969; 1894, **65**, 182) and later workers record m. p. 290° for rubiadin. The acetate crystallised from acetic anhydride in lemon-yellow rods, m. p. 228°, undepressed by an authentic specimen of rubiadin diacetate, m. p. 230°. Schunck and Marchlewski (*loc. cit.*), Simonsen (*J.*, 1920, **117**, 561), and Mitter and Gupta (*J. Indian Chem. Soc.*, 1928, **5**, 25) all record m. p. 225° for this derivative. Methylation as in the previous cases afforded rubiadin dimethyl ether, crystallising from alcohol in lemon-yellow needles, m. p. 160·5°, undepressed by an authentic specimen (Briggs and Dacre, *J.*, 1948, 564).

The rubiadin required for comparison purposes was obtained by demethylation of its 1-methyl ether (*ex C. australis*) (240 mg.) by heating with concentrated sulphuric acid (4 c.c.) at 150° for 10 minutes. The olive-green precipitate (160 mg.), formed on pouring the mixture into water, crystallised from 60% dioxan–water (charcoal) in golden-yellow rods, or from glacial acetic acid as plates of constant m. p. 302°.

Band VI (66 mg.): 3-*Hydroxy-2-methylanthraquinone.*—The compound from this band crystallised from glacial acetic acid in yellow needles which sublimed before melting at 302°, the m. p. recorded by Waldmann and Sellner (*loc. cit.*) for 3-hydroxy-2-methylanthraquinone. This compound (20 mg.) was acetylated as for the other cases described above. After crystallisation from alcohol, 3-acetoxy-2-methylanthraquinone formed long, flat, yellow needles, m. p. 184° (Found: C, 72·5; H, 5·0. Calc. for $C_{17}H_{12}O_4$: C, 72·85; H, 4·3%). Bistrzycki and Zen-Ruffinen (*Helv. Chim. Acta*, 1920, **3**, 378) give m. p. 176°. The original compound and the acetyl derivative were identical (mixed m. p.) with authentic samples supplied by Prof. Mitter.

The original compound (6 mg.) was methylated as described previously. The precipitated product (4·5 mg.), after two crystallisations from alcohol, had m. p. 196°. Waldmann and Sellner (*loc. cit.*) record m. p. 197° for 3-methoxy-2-methylanthraquinone.

The analyses are by Drs. Weiler and Strauss, Oxford, and Mr. R. N. Seelye of this College.

We are indebted to the Chemical Society, the Royal Society of New Zealand, the Australian and New Zealand Association for the Advancement of Science, and the Research Fund Committee of the University of New Zealand for grants, and to Imperial Chemical Industries for gifts of chemicals, and one of us (G. A. N.) to the University of New Zealand for a Duffus Lubecki Scholarship and a Research Fund Fellowship.

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270. *Chemistry of the* Coprosma *Genus. Part V. The Anthraquinone Colouring Matters from* Coprosma acerosa.

By LINDSAY H. BRIGGS and B. R. THOMAS.

From the bark of *Coprosma acerosa* the following compounds have been isolated by chromatography: lucidin, anthragallol 2-methyl ether, anthragallol 1 : 2-dimethyl ether, rubiadin 1-methyl ether and 1 : 6-dihydroxy-2-methylanthraquinone. Rubiadin and 3-hydroxy-2-methylanthraquinone are probably present with another unidentified compound, all three in minute amount. Anthragallol 2-methyl ether, anthragallol 1 : 2-dimethyl ether, and 1 : 6-dihydroxy-2-methylanthraquinone, and probably rubiadin and rubiadin 1-methyl ether, are present also as glycosides.

Coprosma acerosa (Cunningham, *Ann. Nat. Hist.*, 1838, **2**, 207; Oliver, "The Genus Coprosma," *Bernice P. Bishop Museum Bull.*, 132, 1935) is a scrambling shrub with slender interlacing branches forming masses 1—5 feet high. It is characteristic of coastal sand dunes throughout New Zealand and the Chatham Islands to which it is endemic.

A preliminary investigation indicated the presence, in the bark, of both free anthraquinone compounds and their glycosides, and these were extracted separately. The air-dried bark was first extracted with light petroleum. The material which separated after concentration of the extract was dissolved in acetone and adsorbed on calcined magnesia. The light petroleum concentrate contained waxy material and very little of the anthraquinone compounds. The bark was then extracted with benzene from which compound *A* separated on cooling. The residue from the remaining benzene solution was adsorbed from acetone solution on calcined magnesia. Both chromatograms gave the same number of bands of the same colour, and the products of each were then combined. This method of double extraction was preferable to a single extraction with benzene as the light petroleum removed the waxy material which otherwise proved troublesome in the chromatography.

The residual bark was then extracted with alcohol to remove the glycosides. The mixture of yellow solids obtained from the alcoholic solution rapidly changed to a red viscous mass when kept in air, and no crystalline material could be obtained; the material was therefore hydrolysed with dilute sulphuric acid, and the water-insoluble product was then adsorbed on calcined magnesia from acetone solution.

All the chromatograms were produced on a series of separate columns equivalent to one long fully-developed column (cf. Part IV, this vol., p. 1241). The material recovered from individual bands was readsorbed, as before, on smaller columns, and the process repeated, if necessary, until pure chromatograms were obtained.

Compound *A*, which is insoluble in both light petroleum and benzene, does not appear on the chromatogram. The melting points of the purified free compound and its acetate (and the mixed m. p. thereof), its relative insolubility in all common solvents, and its colour reactions indicated identity with lucidin, a trihydroxy-2-methylanthraquinone of uncertain structure obtained from *C. lucida* (Part IV, *loc. cit.*).

The various bands of the chromatograms of the free anthraquinone compounds yielded the following substances. (i) A non-crystalline substance, present in very small amount, which gives a purple colour with alkali and an insoluble barium salt, and may be identical with compound *C* from *C. lucida* (Part IV, *loc. cit.*). (ii) Anthragallol 2-methyl ether, identified by its colour reactions and the melting points of the free compound, its acetate, and methyl ether, and the mixed melting points of the mono- and tri-methyl ethers; it has been found previously only in *C. lucida* (*loc. cit.*) and has been synthesised by Kubota and Perkin (*J.*, 1925, 1894).

(iii) 1 : 6-Dihydroxy-2-methylanthraquinone, identified by analyses and melting points (289°, 215°, and 192°) of the free compound, its acetate, and methyl ether [Simonsen and Rau (*J.*, 1921, **119**, 1339) record m. p.s 281°, 212°, and 182°, respectively, for these compounds, and Bhattacharya and Simonsen (*J. Indian Inst. Sci.*, 1927, **10***A*, 6) m. p. 192° for the dimethyl ether]. This compound also occurs in *C. lucida* (cf. *loc. cit.*, where other occurrences are recorded). (iv) Anthragallol 1 : 2-dimethyl ether, identified by its mixed melting point and that of the acetate; it occurs in *C. lucida* (*loc. cit.*) and in *Oldenlandia umbellata* (Perkin and Hummel, *J.*, 1895, **67**, 823), and has been synthesised by Perkin and Story (*J.*, 1929, 1399). (v) A compound, present in too small amount to be isolated, corresponding in position on the chromatogram and in colour with rubiadin, which is present in much larger amount in *C. lucida* (*loc. cit.*). (vi) Rubiadin 1-methyl ether, identified by its mixed melting point and that of the acetate; it occurs in *C. australis* (cf. *J.*, 1948, 564, where other references to its occurrence and synthesis are given) and *C. areolata* (*J.*, 1948, 568). (vii) Another compound present in too small a quantity for isolation, corresponding in position and colour of the band to 3-hydroxy-2-methylanthraquinone present in *C. lucida* (*loc. cit.*).

The chromatogram of the aglycones from the glycosidic anthraquinones was very similar to that of the free anthraquinone compounds. It consisted of six bands similar to the first six bands of the free compounds, the last band corresponding to 3-hydroxy-2-methylanthraquinone (?) being missing. The amounts isolated sufficed for purification and identification (mixed m. p.s) only in the cases of anthragallol 2-methyl ether, 1 : 6-dihydroxy-2-methylanthraquinone, and anthragallol 1 : 2-dimethyl ether. Two bands corresponded in position and colour with rubiadin and its 1-methyl ether, respectively.

The anthraquinone compounds of *C. acerosa* are thus very similar to those present in *C. lucida*, the principal difference being the presence in *C. lucida* of a much larger proportion of lucidin and a lower level of methylation as shown by the occurrence of free anthragallol and of rubiadin almost entirely unmethylated. This similarity of chemical constituents is in marked contrast with the position of the two species in the phylogenetic relationship proposed by Oliver (*loc. cit.*), which places them in widely differing sections of the genus.

Experimental.

The smooth, reddish bark was collected from mature shrubs in February from Muriwai, both the root and stem bark being used in the investigation. The air-dried, finely ground bark (50-g. lots) was extracted with light petroleum (b. p. 50—70°) in a Soxhlet apparatus for 70 hours, the solvent being kept dry by suspending a small beaker containing calcium chloride at the head of the Soxhlet. The yellow solid which separated from the extract, together with that precipitated from the filtered extract on concentration to 40 c.c., was dissolved in acetone and treated by chromatography on 25-mm. diameter columns of magnesia, freshly heated for 6 hours at a little below dull red heat. Exposure of the magnesia to the atmosphere for 24 hours led to noticeable loss of activity.

The bark was then extracted, as above, with benzene for 70 hours, and the yellow insoluble substance, compound *A*, filtered off after the extract had cooled. The residue from the benzene extract was dissolved in acetone and subjected to chromatography on freshly calcined magnesia. As the bands were the same in number and colour as those in the chromatogram from the light-petroleum extract, the material from both chromatograms was combined.

The residual bark was then extracted with alcohol for 70 hours to remove the glycosides. The residue from the alcoholic extract was dissolved in cold water and filtered through a bed of kieselguhr. The aqueous solution of the glycosides was hydrolysed by heating on the water-bath for 36 hours with 250 c.c. of 10% sulphuric acid, and the precipitate, black through the presence of asperuligenol, was extracted repeatedly with boiling acetone. The acetone solution was then treated by chromatography on freshly calcined magnesia.

All the chromatograms were made as described in Part IV (*loc. cit.*), the whole of the material being absorbed on a series of developed columns equivalent to one long column. The material from each band was liberated by dissolving the magnesia with hydrochloric acid, readsorbed from acetone on a smaller column, and, if necessary, the process was repeated until a pure chromatogram was obtained from each constituent.

Identification of the Free Anthraquinone Compounds from the Chromatogram Bands.—The colour, length of band in a 25-mm. diameter column, and approximate weight of material isolated from a 5-g. sample of bark is recorded for each band.

Band I (blue-grey, 5 mm., —) : compound *B* (unidentified); too little to be purified or identified.

Band II (red, 10 cm., 500—600 mg.) : anthragallol 2-methyl ether. Sublimation at 0·01 mm. afforded yellow needles, m. p. 220°, undepressed by an authentic sample. Only after sublimation could it be crystallised and then only from dioxan. The acetate, from 25 mg., prepared as in Part IV (*loc. cit.*), crystallised from alcohol in yellow prismatic needles, m. p. and mixed m. p. with the diacetate of anthragallol 2-methyl ether, 146°. Likewise, the methylated product from 42 mg., prepared as in Part IV, crystallised from acetone in pale yellow needles, m. p. and mixed m. p. with anthragallol trimethyl ether, 171°.

Band III (dark red, 2 cm., 25—40 mg.) : 1 : 6-dihydroxy-2-methylanthraquinone. After purification by sublimation at 150°/0·01 mm., the material from this band crystallised from alcohol in orange-

yellow needles, m. p. 289° (Found: C, 70·9; H, 4·3; OMe, 0. Calc. for $C_{15}H_{10}O_4$: C, 70·9; H, 3·9%). The diacetate was prepared from the free compound (32 mg.) with acetic anhydride (2 c.c.) and 60% perchloric acid (1 drop) at room temperature during 1 hour. The product obtained on pouring the mixture into water crystallised from alcohol in fine, pale-yellow needles, m. p. 215°, unchanged by recrystallisation (Found: C, 67·35; H, 4·2. Calc. for $C_{15}H_{14}O_5$: C, 67·4; H, 4·1%). The dimethyl ether was prepared as described previously and after two crystallisations from acetone formed yellow rods, m. p. 193° (Found: C, 72·1; H, 5·1; OMe, 17·7. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 4·9; 2OMe, 22·0%).

Band IV (orange, 4 cm., 125—150 mg.): anthragallol 1 : 2-dimethyl ether crystallised from alcohol in yellow, rhombic plates, m. p. and mixed m. p. with authentic material, 238°. The acetate, prepared from 37 mg., as in the case of the 2-methyl ether, crystallised from alcohol in yellow rods, m. p. and mixed m. p. with the authentic acetate, 180—181°.

Band V (dark red, trace, —): compound *F* (unidentified), present in too small a quantity to be isolated or identified.

Band VI (red, 2 mm., 2·5 mg.): rubiadin 1-methyl ether. The light yellow crystalline aggregates obtained from this band, on crystallisation from alcohol, had m. p. 282—284°, undepressed by an authentic specimen, m. p. 286—288°. The product (11 mg.) from this band and the corresponding band from the aglycone chromatogram was acetylated with acetic anhydride (2 c.c.) and 60% perchloric acid (1 drop) at room temperature during 45 minutes. The product, isolated as above, crystallised from alcohol in yellow, flattened, prismatic rods (5·5 mg.), m. p. and mixed m. p. with the authentic acetate, 169—170°.

Band VII (pink, 1 mm., —): compound *I* (unidentified), present in too small a quantity to be isolated or identified.

Identification of the Aglycones of the Anthraquinone Glycosides from the Chromatogram Bands.—The chromatogram of the aglycones of the anthraquinone glycosides contained six bands, I (grey, not eluted with acetic acid–acetone), II (red, 10 cm.), III (dark red, 2 cm.), IV (orange, 4 cm.), V (dark red, 3 mm.), and VI (red, 1—2 mm.). Only from the second, third, and fourth bands was material obtained sufficient for purification and identification. The materials (250 mg.) from the second, the third (40 mg.), and the fourth band (66 mg.) were purified as described previously for the materials isolated from the corresponding bands of the free anthraquinone compounds and were identified with anthragallol 2-methyl ether, 1 : 6-dihydroxy-2-methylanthraquinone, and anthragallol 1 : 2-dimethyl ether, respectively, by mixed melting points.

Analyses are by Drs. Weiler and Strauss.

We are indebted to the Chemical Society, the Royal Society of New Zealand, and the Australian and New Zealand Association for the Advancement of Science for grants, and to Imperial Chemical Industries for gifts of chemicals.

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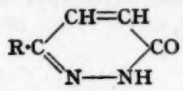
271. *The Conversion of Sucrose into Pyridazine Derivatives. Part VI. The Behaviour of Pyridaz-3-one and its Derivatives towards Aldehydes.*

By HILDA GREGORY, JOAN HILLS, and L. F. WIGGINS.

Neither pyridaz-3-one nor 6-methylpyridaz-3-one gives Mannich bases when treated with formaldehyde and dimethylamine. Instead, a hydroxymethyl group is attached to position 2 of the pyridazone nucleus. Condensation of pyridaz-3-one and of 6-methylpyridaz-3-one with benzaldehyde results in the formation of *phenylbis(pyridaz-3-on-2-yl)methane* and *phenylbis(6-methylpyridaz-3-on-2-yl)methane*, respectively. Experiments which indicate the structure of these compounds are described.

IN an attempt to prepare Mannich bases from 6-methylpyridaz-3-one (I; R = Me) obtained from lævulic acid (Overend and Wiggins, *J.*, 1947, 239), the compound was treated with formaldehyde and dimethylamine hydrochloride according to Mannich and Kather's procedure (*Arch. Pharm.*, 1919, **257**, 18) for the preparation of Mannich bases from antipyrine. A crystalline compound was isolated, which was not a Mannich base since it did not contain a dimethylamine residue. Moreover, it was very unstable and readily liberated formaldehyde when heated alone or boiled with water. That dimethylamine was not involved in the reaction was proved by the fact that the same compound was isolated when piperidine was used instead of dimethylamine. In fact, it was later found that the presence of a secondary base was not essential to the reaction, since 6-methylpyridaz-3-one and aqueous formaldehyde gave the same compound, on being heated together. Owing to the instability of the compound, a molecular-weight determination by ebulloscopic methods was impracticable. By the *X*-ray method, however, a value of either 254 or 127 was obtained, and application of Barger's method for the determination of molecular weight indicated the latter as the correct value. This and ultimate analysis showed the compound to be a hydroxymethyl derivative of 6-methylpyridaz-3-one.

That the methyl group at position 6 was not involved in the reaction was indicated by the fact that a very similar compound was isolated when pyridaz-3-one (I; R = H) itself was heated with formaldehyde solution. The hydroxymethyl group may therefore be attached to the nitrogen atom at position 2 of the pyridazone nucleus (II; R = CH_2·OH) or be combined with the hydroxyl group of the enolic form of (I; R = Me) in hemi-acetal formation as shown by (III; R = O·CH_2·OH). Formulæ (IV) and (V) are also possible but very improbable because a hydroxymethyl group attached to the pyridazone nucleus by a carbon to carbon bond is very unlikely to be removed by warming with water.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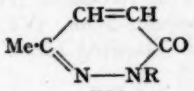
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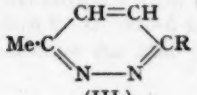
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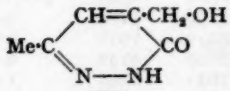
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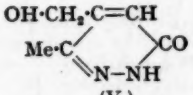
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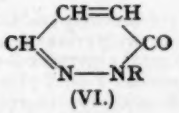
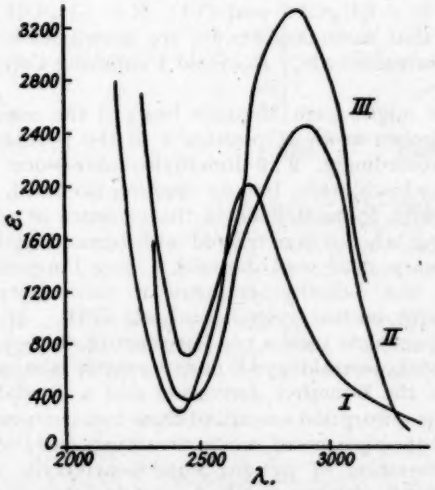

(VI.)

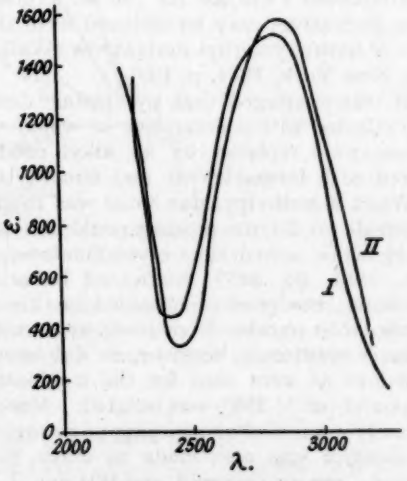
Hence, there are two possible formulæ for the hydroxymethyl derivative obtained from 6-methylpyridaz-3-one, namely (II; R = CH_2·OH) and (III; R = O·CH_2·OH). A decision

FIG. 1.



I. 3-*Methoxy-6-methylpyridazine.*
II. 2 : 6-*Dimethylpyridaz-3-one.*
III. 6-*Methyl-2-hydroxymethylpyridaz-3-one.*

FIG. 2.



I. 2-*Hydroxymethylpyridaz-3-one.*
II. 2-*Methylpyridaz-3-one.*

between these two possibilities has been made by a study of the absorption spectra of the condensation product and related pyridazone derivatives. 6-Methylpyridaz-3-one can be alkylated at position 2 with methyl iodide and sodium methoxide, and the constitution of this as 2 : 6-dimethylpyridaz-3-one (II; R = Me) has been proved by synthesis (Overend and Wiggins, forthcoming publication).

On the other hand, when 3-chloro-6-methylpyridazine (III; R = Cl) is treated with sodium methoxide, an isomeric compound with entirely different properties is obtained. This, by its method of preparation, must be 3-methoxy-6-methylpyridazine (III; R = OMe).

2 : 6-Dimethylpyridaz-3-one shows selective absorption of light in the ultra-violet at λ 2940 A. ($\varepsilon_{max.}$ 2460), whereas 3-methoxy-6-methylpyridazine shows absorption at λ 2710 A. ($\varepsilon_{max.}$ 2000) (see Fig. 1). Now the hydroxymethyl derivative of 6-methylpyridaz-3-one shows a very similar absorption spectrum to that of 2 : 6-dimethylpyridaz-3-one with optimum absorption at λ 2890 A. ($\varepsilon_{max.}$ 3340). Hence it would appear that the compound, m. p. 131°, is 6-*methyl*-2-*hydroxymethylpyridaz*-3-*one* (II; R = CH_2·OH).

A similar conclusion is reached when the hydroxymethyl derivative of 3-pyridazone itself

is studied. Its absorption spectrum shows a band very similar to that of its homologue described above, but the absorption peak is displaced a little towards the ultraviolet (λ 2820 A.). A comparison of its spectrum with that of 2-methylpyridaz-3-one (VI; R = Me) (λ 2860 A.), obtained by alkylation of pyridaz-3-one with methyl iodide and sodium methoxide, indicates that the two compounds have essentially the same structure (see Fig. 2). In addition, comparison of the spectra of 2 : 6-dimethyl- and 2-methyl-pyridaz-3-one with those of the hydroxymethyl derivatives of 6-methylpyridaz-3-one and pyridaz-3-one shows that removal of the methyl group at position 6 of the pyridazone nucleus results in a displacement of the absorption peak towards the ultra-violet of 70—80 A. Hence, the hydroxymethyl derivative of pyridaz-3-one is 2-*hydroxymethylpyridaz-3-one* (VI; R = CH_2·OH). The ultra-violet absorption data are summarised in the following table.

Compound.	λ, A.	$\varepsilon_{max.}$	Concn. in EtOH, mg. per 100 c.c.
3-Benzyloxy-6-methylpyridazine	2730	1480	8·4
2-Benzyl-6-methylpyridaz-3-one	3010	1618	8·5
Phenyldi-(6-methylpyridaz-3-on-2-yl)methane	2980	4759	6·7
Phenyldi-(pyridaz-3-on-2-yl)methane	2930	5364	1·43
3-Methoxy-6-methylpyridazine	2710	2000	4·5
2 : 6-Dimethylpyridaz-3-one	2940	2460	7·48
6-Methyl-2-hydroxymethylpyridaz-3-one	2890	3340	4·2
2-Hydroxymethylpyridaz-3-one	2820	1512	6·15
2-Methylpyridaz-3-one	2860	1538	9·37

Additional evidence for the structures (II; R = CH_2·OH) and (VI; R = CH_2·OH) for these derivatives may be adduced from the fact that secondary amines are known readily to form *N*-hydroxymethyl derivatives (Walker, "Formaldehyde," Reinhold Publishing Corporation, New York, 1944, p. 199).

It was envisaged that pyridazone derivatives might form Mannich bases if the reaction were effected with a derivative in which the hydrogen atom at position 2 of the pyridazone nucleus were replaced by an alkyl residue. Accordingly, 2 : 6-dimethylpyridaz-3-one was treated with formaldehyde and dimethylamine hydrochloride, but no reaction occurred.

When 6-methylpyridaz-3-one was condensed with formaldehyde in the presence of acetic anhydride no definite product could be isolated, but when it was treated with benzaldehyde in boiling acetic anhydride a crystalline compound (m. p. 207°) was obtained. Since Poppenberg (*Ber.*, 1901, **34**, 3257) condensed benzaldehyde and 6-methylpyridazine to form 6-styrylpyridazine, the product obtained in this case might be 6-styrylpyridaz-3-one (VII). If this were so, then pyridaz-3-one itself would not be expected to yield a condensation product under similar conditions; however, it did condense with benzaldehyde under exactly the same conditions as were used for the condensation of the 6-methyl derivative and a crystalline compound (m. p. 239°) was isolated. Moreover, the absorption spectra of these two compounds so closely resembled one another as to suggest that they possessed similar structures (see Fig. 3). An attempt was also made to effect the condensation of pyridaz-3-one-6-carboxylic acid (Homer, Gregory, Overend, and Wiggins, *J.*, 1948, 2195) with benzaldehyde, but decarboxylation occurred and the same compound as was obtained from pyridaz-3-one was isolated.

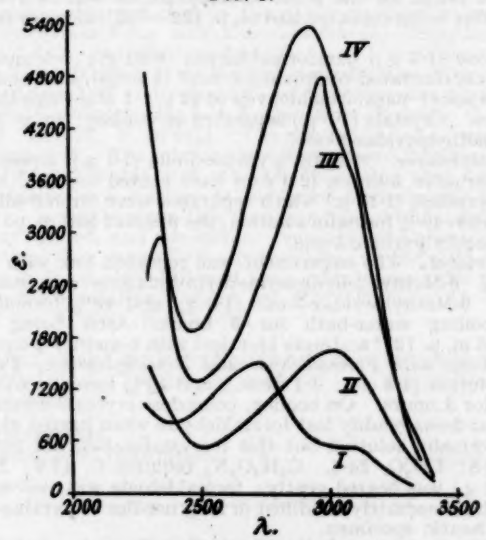
Determination of the molecular weight of these two condensation products showed them both to contain two pyridazone residues and one phenyl group, and ultimate analysis showed that benzaldehyde had condensed with two molecules of each pyridazone with elimination of one molecule of water.

Since the condensation does not involve the methyl group of 6-methylpyridaz-3-one it must take place through the attachment of the benzylidene group to either C_4 or C_5, to the nitrogen atom at position 2, or to the hydroxyl group at C_3 of the enolic form of the pyridazone nucleus. The compound, however, is not very stable, for it is readily decomposed by aqueous acids with the liberation of benzaldehyde. This would indicate that structures of the type (VIII) are unlikely, as it would be expected that if C–C bonds were involved in the linkage of benzaldehyde and 6-methylpyridaz-3-one then they would be resistant to these conditions of hydrolysis. Moreover, attachment of the benzylidene group at C_4 or C_5 would leave the pyridazone residues liable to *N*-alkylation at position 2. This does not occur. In addition, condensation does not occur with benzaldehyde when position 2 is alkylated. For instance, 2 : 6-dimethylpyridaz-3-one does not condense with benzaldehyde under the same conditions.

Hence, two possible structures remain for these condensation products, *i.e.*, (IX) and (X), where R = Me or H. In fact, the structure phenyldi-(6-methylpyridaz-3-on-2-yl)methane

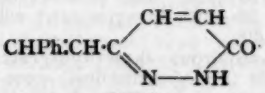
(X; R = Me) has been assigned to the condensation product of benzaldehyde and 6-methylpyridaz-3-one by a comparison of its absorption spectrum with those of compounds having the type of structure shown by (IX) and (X) (R = Me). The two compounds showing most resemblance to (IX) and (X) and with which a comparison could justly be made were 2-benzyl-6-methylpyridaz-3-one, obtained by Homer and Wiggins (forthcoming publication), and *3-benzyloxy-6-methylpyridazine*, prepared by the treatment of 3-chloro-6-methylpyridazine with sodium benzyloxide.

FIG. 3.



I. *3-Benzyloxy-6-methylpyridazine.*
II. *Benzyl-6-methylpyridaz-3-one.*
III. *Phenyldi-(6-methylpyridaz-3-on-2-yl)methane.*
IV. *Phenyldi(pyridaz-3-on-2-yl)methane.*

The condensation product of 6-methylpyridaz-3-one with benzaldehyde showed maximum absorption at λ 2980 A. ($\varepsilon_{max.}$ 4759), whereas 2-benzyl-6-methylpyridaz-3-one showed maximum absorption at approximately the same wave-length (λ 3010 A.) but with a much lower intensity



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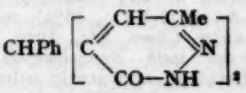
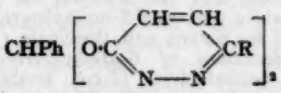
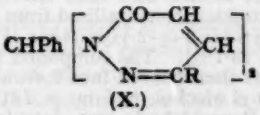


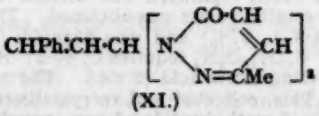
(VIII.)



(IX.)



(X.)



(XI.)

($\varepsilon_{max.}$ 1618). On the other hand, 3-benzyloxy-6-methylpyridazine showed absorption at λ 2730 A. ($\varepsilon_{max.}$ 1480) (see Fig. 3). Hence structure (X; R = Me) is assigned to the product of m. p. 207°.

The condensation product of benzaldehyde with pyridaz-3-one itself is considered to have an analogous structure and to be *phenyldi(pyridaz-3-on-2-yl)methane* (X; R = H) on account of the similarity of its absorption spectrum with that of the analogous condensation product from 6-methylpyridaz-3-one (see Fig. 3). The absence of the 6-methyl group in (X; R = H) results in the expected shift of the head of the absorption band towards the ultra-violet by 50 A. (see table).

A similar compound was obtained when cinnamaldehyde was condensed with 6-methylpyridaz-3-one, and by analogy with the foregoing compounds it is believed to be *styryldi-(6-methylpyridaz-3-on-2-yl)methane* (XI).

Experimental.

Condensation of 6-Methylpyridaz-3-one with Formaldehyde.—(*a*) *In presence of dimethylamine hydrochloride.* The procedure used was that of Mannich and Kather (*loc. cit.*). 6-Methylpyridaz-3-one (1·5 g.), dimethylamine hydrochloride (1·2 g.; 1 mol.), 40% formalin solution (1·2 c.c.; 1 mol.), and water (10 c.c.) were shaken together for 24 hours. The crystals which had separated were filtered off; m. p. 125—128° (yield, 0·7 g.). The product readily lost formaldehyde when heated alone or in solvents, thus rendering recrystallisation difficult. It was finally recrystallised from 40% formalin solution; m. p. 131°. It was *6-methyl-2-hydroxymethylpyridaz-3-one* (Found: C, 51·3; H, 5·8; N, 20·4; CH_2O, 21·8. $C_6H_8O_2N_2$ requires C, 51·4; H, 5·7; N, 20·0; CH_2O, 21·4%). The product (0·3 g.) in water (1·0 c.c.) was heated under reflux for one hour. Formaldehyde was evolved, and on cooling crystals (0·19 g.) separated which after being collected had m. p. 122—123°, alone or in admixture with 6-methylpyridaz-3-one.

(*b*) 6-Methylpyridaz-3-one (1·5 g.), paraformaldehyde (0·62 g.; 1·5 mols.), dimethylamine hydrochloride (1·2 g.; 1 mol.), concentrated hydrochloric acid (1 drop), and absolute alcohol (3 c.c.) were heated under reflux for one hour; paraformaldehyde (0·42 g.; 1 mol.) was then added, and the mixture heated for a further 2 hours. Crystals (1·5 g.) separated on cooling; m. p. 131°, alone or in admixture with 6-methyl-2-hydroxymethylpyridaz-3-one.

(*c*) *In presence of dimethylamine.* 6-Methylpyridaz-3-one (1·1 g.), aqueous dimethylamine solution (25%; 2 c.c.), and 40% formalin solution (2·0 c.c.) were heated together on a boiling water-bath for 3 hours. On cooling, the crystals (1·13 g.) which separated were filtered off and had m. p. 126—128°. After being recrystallised from 40% formalin solution, the product had m. p. 131°, alone or in admixture with 6-methyl-2-hydroxymethylpyridaz-3-one.

(*d*) *In presence of piperidine.* The experiment was repeated but with a few drops of piperidine instead of dimethylamine. 6-Methyl-2-hydroxymethylpyridazone was isolated in 60% yield.

(*e*) *Without a catalyst.* 6-Methylpyridaz-3-one (1·0 g.) and 40% formalin solution (4·0 c.c.) were heated together on a boiling water-bath for 3 hours. After being kept overnight, crystals (0·8 g.) separated which had m. p. 131° and were identical with 6-methyl-2-hydroxymethylpyridaz-3-one.

Treatment of Pyridaz-3-one with Formaldehyde and Dimethylamine.—Pyridaz-3-one (2·0 g.), 26% aqueous dimethylamine solution (4·4 c.c.; 1·1 mols.), and 40% formalin solution (10 c.c.) were heated together on a water-bath for 3 hours. On cooling, colourless crystals separated (1·95 g.); m. p. 142°. This *2-hydroxymethylpyridaz-3-one* readily lost formaldehyde when heated alone or in solvents. It was recrystallised from 40% formalin solution but this recrystallisation did not raise the m. p. (Found: C, 47·9; H, 4·98; N, 22·8; CH_2O, 24·4. $C_5H_6O_2N_2$ requires C, 47·6; H, 4·76; N, 22·2; CH_2O, 23·8%). The product (0·1 g.) was heated gently; formaldehyde was evolved and the residue distilled as a colourless liquid which immediately solidified in long needles of pyridaz-3-one, m. p. 103°, alone or in admixture with an authentic specimen.

X-*Ray Examination of 2-Hydroxymethylpyridaz-3-one.*—By means of single-crystal rotation and oscillation photographs the following cell dimensions were obtained: $a = 13·6$, $b = 11·35$, $c = 7·39$ A.; space group *pcab*. From the observed density, 1·478 g./c.c., the molecular weight was calculated to be $1016/n$, where n may be either 4 or 8; an approximate molecular-weight determination by Barger's method (*J.*, 1904, **85**, 286) indicated the lower molecular weight, whence $n = 8$, and the appropriate molecular weight of 2-hydroxymethyl-3-pyridazone is therefore 127 (Calc.: 126).

2-Methylpyridaz-3-one.—To pyridaz-3-one (4·0 g.) dissolved in dry methyl alcohol were added methyl iodide (4·0 c.c.) dissolved in the same solvent and then a dry methyl-alcoholic solution of sodium methoxide (4·5 g.). The mixture was heated under reflux for 2 hours and then evaporated almost to dryness. Water was added, and the solution extracted with benzene. The dried extract was evaporated, and the residual oil distilled at 220° (bath temp.)/10 mm. The product solidified immediately and was 2-methylpyridaz-3-one (2·1 g.; 46%), m. p. 38—39°, in agreement with that recorded by Evans and Wiselogle (*J. Amer. Chem. Soc.*, 1945, **67**, 60).

Condensation of 6-Methylpyridaz-3-one with Benzaldehyde.—Anhydrous 6-methylpyridaz-3-one (5·0 g.), benzaldehyde (7 c.c., freshly distilled), and acetic anhydride (5 c.c., redistilled) were heated together under reflux for 16 hours. Excess of benzaldehyde was removed by steam-distillation, the viscous brown oil which separated was washed with a little alcohol and then triturated with ether, whereby a semi-crystalline mass was obtained. The crude product, recrystallised from aqueous alcohol, had m. p. 207° (1·9 g., 27%) and was *phenyldi-(6-methylpyridaz-3-on-2-yl)methane* (Found: C, 66·1; H, 5·3; N, 17·6. $C_{17}H_{16}O_2N_4$ requires C, 66·2; H, 5·2; N, 18·1%). The compound (0·5 g.) was kept overnight with fuming nitric acid (2 c.c.). The mixture was then poured into ice-water, and a white solid separated. This, collected and recrystallised from ethyl alcohol, had m. p. 121—122°, alone or in admixture with 6-methylpyridaz-3-one monohydrate. Benzaldehyde was detected in the acidic mother-liquors.

Non-methylation of Phenyldi-(6-methylpyridaz-3-on-2-yl)methane.—To the condensation product (1·0 g.) in dry methyl alcohol, were added a solution of sodium methoxide (0·2 g.; 1 mol.) in dry methyl alcohol and then methyl iodide (1·7 g.; 1·5 mols.), and the mixture was heated under reflux for one hour. The solution was evaporated nearly to dryness under reduced pressure, a little water added, and the aqueous solution extracted with benzene. The extract was dried ($MgSO_4$), evaporated to dryness, and the residue recrystallised from aqueous alcohol; m. p. 207° alone or in admixture with the starting material (yield, 0·9 g.).

Condensation of Pyridaz-3-one with Benzaldehyde.—Anhydrous pyridaz-3-one (3·0 g.), benzaldehyde (3 c.c., freshly distilled), and acetic anhydride (3 c.c.) were heated together under reflux for 20 hours. Thereafter, the mixture was cooled, alcohol and water added to the syrup, and the crystalline mass obtained was filtered off. Recrystallised from alcohol, it formed colourless needles of *phenyldi(pyridaz-3-on-2-yl)methane*, m. p. 239° (2·0 g.) (Found: C, 64·3; H, 4·3; N, 20·0. $C_{15}H_{12}O_2N_4$ requires C, 64·3; H, 4·3; N, 20·0%).

Condensation of Pyridaz-3-one-6-carboxylic Acid with Benzaldehyde.—Anhydrous pyridaz-3-one-6-

carboxylic acid (2·0 g.), benzaldehyde (4 c.c.), and acetic anhydride (2·5 c.c.) were heated together under reflux for 20 hours. Excess of benzaldehyde was removed by steam-distillation, and the solid which separated was collected and recrystallised from aqueous alcohol; m. p. 239° alone or in admixture with the phenyldi(pyridaz-3-on-2-yl)methane obtained as above.

Oxidation of Phenyldi-(6-methylpyridaz-3-on-2-yl)methane.—The substance (1·8 g.) was dissolved in concentrated sulphuric acid (18 c.c.). The solution was mechanically stirred and the temperature kept at *ca.* 20° whilst finely ground potassium dichromate (1·1 mols.) was added slowly in portions. When the addition was complete, stirring was continued for another hour, the resulting green mixture was poured on ice, and the mixture set aside for several hours. A white solid separated (0·3 g.), which was filtered off and recrystallised from water. It had m. p. 257°, alone or in admixture with pyridaz-3-one-6-carboxylic acid. Benzaldehyde was detected in the acidic mother-liquors.

Condensation of 6-Methylpyridaz-3-one with Cinnamaldehyde.—Anhydrous 6-methylpyridaz-3-one (11·0 g.), cinnamaldehyde (7 c.c.), and acetic anhydride (7 c.c.) were heated together on an oil-bath under reflux for 12 hours. The mixture was cooled and made alkaline with sodium hydroxide; a white solid separated, which was filtered off and recrystallised from aqueous alcohol (yield, 2·1 g.). It had m. p. 239° and was *styryldi-(6-methylpyridaz-3-on-2-yl)methane* (Found: C, 68·6; H, 5·34; N, 16·8. $C_{19}H_{18}O_2N_4$ requires C, 68·3; H, 5·39; N, 16·8%). The compound (0·3 g.) was kept at room temperature for 2 hours with fuming nitric acid. The mixture was then poured into ice–water; no solid separated, but cinnamaldehyde was detected in the acid solution, indicating that decomposition had occurred.

3-Benzyloxy-6-methylpyridazine.—A mixture of 3-chloro-6-methylpyridazine (5·0 g.), benzyl alcohol (4·1 c.c.), and sodium (0·9 g.) in dry benzene (100 c.c.) was heated under reflux for 3 hours. The dark brown reaction mixture was filtered, and the solvent evaporated to give a viscous syrup which partly crystallised. The product was then pressed on a porous tile, and the solid obtained recrystallised first from alcohol–light petroleum (b. p. 40—60°) and then from ether–light petroleum. The colourless needles of *3-benzyloxy-6-methylpyridazine* had m. p. 105° (Found: C, 71·8; H, 6·17; N, 13·4. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0; N, 14·0%).

Our thanks are due to the Colonial Products Research Council for supporting this investigation, and to Drs. R. W. H. Small and J. C. Tranter for carrying out the molecular-weight determinations on 2-hydroxymethylpyridaz-3-one.

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272. *Hydrothermal Reactions involving Thallium.*

By H. F. W. TAYLOR.

Mixtures of thallous aluminate, silicate, and aluminosilicate compositions have been subjected to hydrothermal treatment at temperatures of 200—350°. Analytical, optical, and *X*-ray powder examinations of the insoluble products have shown that several crystalline species can be obtained in a reproducible manner. Analyses of one species approximated to $TlAlSiO_4$, analogous to kaliophilite and kalsilite ($KAlSiO_4$), but the *X*-ray powder spacings differed considerably from those of either of the potassium minerals. α-Cristobalite and α-quartz were obtained from the silica-rich mixtures, but only in the absence of alumina. A species $TlAlSi_2O_6$, obtained in good yield from mixtures of approximately its own composition, readily underwent base exchange and showed a close structural similarity to leucite ($KAlSi_2O_6$) or analcite ($NaAlSi_2O_6.H_2O$), into which it could readily be converted. Thus univalent thallium can at least to a limited extent form aluminosilicates in which its rôle resembles closely that of sodium or potassium.

UNIVALENT thallium shows a considerable likeness to the alkali metals, and it might therefore be expected to form crystalline aluminosilicates comparable with the zeolites, sodalites, or other groups of minerals containing alkali metals. However, no natural aluminosilicates are known which contain more than a trace of thallium, and although the literature contains isolated references to laboratory preparations of silicates (Fleming, *Jena Zeit.*, 1868, **4**, 33; Wyrouboff, *Bull. Soc. min.*, 1889, **12**, 536) and an aluminate (Hawley, *J. Amer. Chem. Soc.*, 1907, **29**, 300) and to the introduction of thallium into zeolites by base exchange (Steiger, *Amer. J. Sci.*, 1902, **14**, 31), no attempts to obtain crystalline thallium aluminosilicates by synthesis appear to have been recorded. In the case of the alkali metals, on the other hand, a variety of aluminosilicates have been obtained synthetically under hydrothermal conditions (*e.g.*, Morey and Ingerson, *Econ. Geol.*, 1937, **32**, 607), reactions in alkaline media at temperatures below 350° often having yielded zeolites or similar minerals (see, *e.g.*, Barrer, *J.*, 1948, 127, 2158). The possibilities of preparing thallous aluminosilicates by similar methods have therefore been partly explored in the present investigation.

Treatment of a mixture of composition Tl_2O,Al_2O_3 with either water or excess of thallous hydroxide solution yielded no crystalline products either at 200° or at 300°. Mixtures of composition $Tl_2O,nSiO_2$ or $Tl_2O,Al_2O_3,nSiO_2$, on the other hand, yielded the crystalline species

described below. Each species could be obtained reproducibly under the conditions defined in the table.

Species A. Spheroidal particles showing no definite faces; diameter about 15μ; isotropic or nearly so; $n = 1{\cdot}490$. Subsequently identified as α-cristobalite.

Species B. Rods or prisms, up to 10μ in length, occurring singly, in bundles, or rosettes; positive elongation and straight extinction; apparently uniaxial, with $\omega = 1{\cdot}755$, $\varepsilon = 1{\cdot}78$. Readily gelatinised by acids.

Species C. Spheroidal particles showing no definite faces; diameter up to 35μ; usually isotropic or nearly so; $n = 1{\cdot}645$. Sometimes fringed with crystals, apparently of species B; stable to cold acids. Subsequently identified as the thallium analogue or near-analogue of analcite or leucite.

Species D. Ill-formed rods; extinction straight or nearly so, with positive elongation; birefringent; mean refractive index 1·64.

Species E. Birefringent plates of mean refractive index 1·70. Tends to form multiple twins. Species D and E were never obtained in major yields.

Discussion.—The mixtures of thallous silicate composition yielded, at temperatures up to 300°, no crystalline products other than A, which was identified by its optical properties and *X*-ray powder photographs as α(low)-cristobalite. This was formed in the highest yield when $n = 8$ or 10 and $T = 300°$; at 350°, however, a mixture of composition $Tl_2O,10SiO_2$ gave α-quartz. These results are in general accordance with those of Wyart (*Bull. Soc. franç. Min.*, 1943, 479), who investigated the hydrothermal crystallisation of silica from water or potassium hydroxide solutions. It also seems probable from the foregoing observations that neither aluminates nor silicates of thallium are likely to be formed under the conditions of the present investigations.

*Crystalline products of hydrothermal reactions.**

Composition of mixture:	$Tl_2O,nSiO_2$.	$Tl_2O,Al_2O_3,nSiO_2$.			
Medium:	Water.	Water.	Water.	TlOH, aq.	TlOH, aq.
Temp.:	300°	220°	300° or 310°	220°	310°
n.					
1	Poor crystn. (9·5) †	Good B (9·8)	Moderate B (9·5)	Good B; trace D (10·5)	Poor xtal'n. (10·5)
2	Rare A (10·0)	Mod. B; trace C (7·8)	Good B; trace C (7·8)	V. good B; fair C & D (10·5)	Good B; traces C & D (10·5)
3	Rare A (9·5)	Mod. B; poor C (7·0)	Mod. B; poor C (7·2)	V. good B; poor C & mod. D (10·5)	Good B; poor C & D (10·5)
4	Rare A (9·5)	Rare B; good C (8·0)	Poor B; v. good C (7·0—8·0)	Good B & C; mod. D (10·5)	Mod. B, C; poor D (10·5)
5	Rare A (9·5)	Rare B; good C (8·5—9·5)	Poor B & D; v. good C (7·0—8·0)	Good C; poor B & D (10·5)	Mod. B & C; poor D & E (9·8)
6	Mod. A (9·5)	Mod. C (9·0—9·5)	Mod. C (7·0—8·0)	Good C (10·5)	Good C, poor D, Rare B & E (9·8—10)
8	Good A ‡ (9·5)	Poor C—nil (8·5—9·0)	Poor—mod. C (6·5—7·5)	Poor C (10·0)	Rare B & D, mod. C (9·8—10·0)
10	Good A ‡ (9·5)	Nil (8·5)	Nil (7·5)	V. poor C (10·0)	V. poor C (10·0)
Ref.: §	*a*	*b*	*c*	*d*	*e*

* Where crystallisation is described as poor, nil, etc., considerable amorphous matter was present in the product.

† Figures in parentheses denote pH values of the cold mother-liquors after reaction.

‡ At 200° little or no crystallisation took place from these mixtures.

§ Used subsequently, with *n* to denote the product of a given experiment; thus that obtained from a mixture of composition $Tl_2O,Al_2O_3,5SiO_2$ treated with water at 300° would be 5*c*.

Mixtures of the general composition $Tl_2O,Al_2O_3,nSiO_2$ yielded, on hydrothermal treatment with water at 300°, B as the major product at the lower values of *n*, and C at intermediate

values. At the highest values studied (*i.e.*, up to $n = 10$), optical and *X*-ray examination showed that, in contrast to the results obtained in the absence of alumina, little or no crystallisation had occurred. In particular, no quartz or cristobalite was ever formed in these experiments from the mixtures containing alumina. Reduction of the temperature to 220° has only a minor effect on these results.

Attempts to obtain B entirely free from amorphous matter and traces of C were unsuccessful, although microscopic examination showed that the products obtained when $n = 2$ contained a high proportion of this species. Chemical analyses of these materials gave results not incompatible with the empirical formula $TlAlSiO_4$ for B, and the 1 : 1 ratio of Tl to Al received some further support from the fact that the composition of the product, and the high yield of *B*, were substantially unaltered if a mixture of appropriate composition was crystallised, not from water, but from an excess of aqueous thallous hydroxide. Two potassium compounds of the corresponding formula ($KAlSiO_4$) have been prepared hydrothermally from mixtures of analogous composition, kaliophilite by Thugutt (*Arch. Min. Soc. Varsovie*, 1937, **13**, 109) and others, and kalsilite by Wyart (*Compt. rend.*, 1947, **225**, 944). Comparison of the *X*-ray powder data did not, however, reveal any striking similarities in spacing as between B and any of the three known forms of $KAlSiO_4$ (cf. Bannister and Hey, *Min. Mag.*, 1942, **26**, 218, and private communication; Rigby and Richardson, *ibid.*, 1947, **28**, 75) except for the spacing close to 3·10 A. which is well marked in all four cases. There is thus as yet an inadequate basis for speculation regarding the structural type of B.

Identity of C with the product obtained by base exchange of analcite with thallous nitrate is indicated by analytical, optical, and *X*-ray data. Species C could be obtained in a fairly pure condition, and analysis indicated the composition $Tl_2O,Al_2O_3,4SiO_2$. Steiger (*loc. cit.*) found that virtually complete replacement of the sodium in analcite could be brought about by treatment in a sealed tube with thallous nitrate at 220°; this was confirmed by the author, and the crystal form, refractive index, and powder photograph of the product were identical with those of C. Furthermore, three successive treatments of the latter with 20% sodium nitrate solution at 250° leached out a total of about 70% of the thallium present, and the refractive indices of the crystals fell gradually to a minimum value close to that of natural or synthetic analcite. *X*-Ray powder photographs and chemical analysis confirmed the view that this product contained a high proportion of analcite.

The fact that C forms mixed crystals with analcite, together with the apparent coincidence of its spacings with those of analcite, shows that there must be a considerable similarity in structure. On the other hand, as Steiger (*loc. cit.*) pointed out, its anhydrous character may indicate an even closer similarity to leucite.

Replacement of water by thallous hydroxide in the hydrothermal treatment of thallous aluminosilicate mixtures extends the range of formation of B to higher values of n, while yields of the minor products D and E are increased. *X*-Ray powder photographs of the products richest in these species showed, however, no lines that could not be attributed to either B or C. It is likely that neither D nor E was ever present in sufficient proportion to be apparent in a powder photograph, although it is possible that their strongest spacings may have coincided with spacings of B or C. The nature of D and E is obscure.

Experimental.

Materials.—Thallous oxide was used in the form of aqueous hydroxide, freshly prepared from thallous sulphate and barium hydroxide, moderate precautions being taken to exclude carbon dioxide. Alumina ($Al_2O_3,3H_2O$) was obtained by the action of cold water on amalgamated aluminium (Wislicenus, *Z. angew. Chem.*, 1904, **17**, 805; Weiser and Milligan, *Chem. Reviews*, 1939, **25**, 1); after washing with alcohol and ether and air-drying, ignition loss = 34·5% (theoretical). *X*-Ray powder photographs showed only a few diffuse arcs, very weak when filtered radiation was used; these were not observed on subsequent photographs. The silica was a moist gel, supplied by Messrs. B.D.H., Ltd., containing approximately 15% of SiO_2; extraction with water at 220° yielded a neutral solution free from common inorganic ions. *X*-Ray powder photographs gave no indication of crystalline character.

Preparative Methods.—Each mixture for hydrothermal treatment was prepared from appropriate quantities of the constituents by careful evaporation in a current of carbon dioxide-free air until a white powder was obtained which was sufficiently dry to be ground in a mortar; the product was weighed and kept in a well-stoppered bottle.

Hydrothermal reactions were carried out in stainless-steel autoclaves of approximately 18 c.c. capacity, similar to those described by Barrer (*loc. cit.*). In each case a quantity of mixture containing the equivalent of 2 millimols. of Tl_2O was treated with 10 ml. of water or 0·233N-TlOH. An electric oven thermostatically controlled to $\pm 1°$ was used for most of the reactions, the duration of which was 36—60 hours; no significant influence on the results could be traced to variations in the time of heating within these limits.

After heating, each autoclave was cooled and opened, and the approximate pH value of the liquor

determined colorimetrically as one factor governing reproducibility. The solid residue was filtered off and washed thoroughly with water, alcohol, and ether.

Optical and X-Ray Examination.—Optical investigations were made with a Leitz polarising microscope. Refractive indices, which were measured in white light and at room temperature, are accurate to about ±0·005. *X*-Ray data were obtained by means of a Hilger HRX diffraction unit with a 9-cm. powder camera, filtered Cu-*K*α radiation and 2—4 hour exposures being used throughout. Heavy background intensities and errors in spacing, due to the strong absorption of thallium towards *X*-rays, could be appreciably reduced by dilution of the specimen with gum arabic. Intensities were estimated visually.

Chemical Analysis.—This presents certain difficulties in the case of silicates containing thallium, which are, however, minimised when, as in the present case, acids can be used to effect decomposition. Silica, alumina, thallous oxide, and, where present, sodium oxide were determined on one sample of 0·5—1·0 g. as follows. The sample was decomposed on the water-bath with 70% nitric acid. This presented no difficulty with species B, but C required preliminary grinding followed by prolonged treatment (8—12 hours) with nitric acid. Silica was determined by the standard method, two evaporations being carried out; it should, however, be noted that thallium, as well as silica, may be volatilised by treatment with hydrofluoric and nitric acid. The solution was again evaporated, and the residue taken up in a minimum quantity of dilute nitric acid, reduced by passage of sulphur dioxide, and thallium precipitated as iodide followed by alumina as such. When sodium had to be determined, a freshly prepared solution of ammonium iodide was used to precipitate the thallium, and the sodium was afterwards weighed as sulphate. All analytical results are expressed in terms of the dry weight at 110°.

Species A. Two preparations of 10*a* gave almost identical *X*-ray data, *viz.*, 4·16s, 3·56w, 3·27w, 2·85vw, 2·52w, 2·17w, 2·06w, 1·95w, 1·89vw, 1·62w. Except for the weak spacing 3·56, these agree with data quoted by Hanawalt, Rinn, and Frevel (*Ind. Eng. Chem. Anal.*, 1938, **10**, 457) for α-cristobalite. A similar growth of α-cristobalite was observed when thallous carbonate replaced thallous hydroxide. The preparation of quartz obtained at a higher temperature showed 43 spacings all in agreement with published values (*loc. cit.*).

Species B. Analyses of specimens 2*b*, 2*c*, and 2*e* gave respectively the following results: Tl_2O, 60·0, 62·9, 63·4; Al_2O_3, 18·8, 16·7, 14·5; SiO_2, 20·9, 20·1, 23·1; totals 99·7, 99·7, 101·0 (Calc. for $Tl_2O,Al_2O_3,2SiO_2$ and $Tl_2O,Al_2O_3,3SiO_2$, respectively: Tl_2O, 65·7, 60·1; Al_2O_3, 15·7, 14·4; SiO_2, 18·6, 25·5%). Since all specimens contained traces of C, the analyses may be considered to support the former rather than the latter formula. *X*-Ray powder photographs of specimens 2*b* (two preparations) and 2*e* showed no significant discrepancies and gave the following mean data: (6·50vw), 4·81ms, 4·24vw, 3·31ms, 3·11s, 2·96mw, 2·71m, 2·36vw, 2·28w, 2·19vw, 2·09m, 1·985mw, 1·890mw, 1·840w, 1·780vww, 1·705mw, 1·645mw, 1·625vw, 1·555vw, 1·520vw, (1·500vvw), 1·465vvw, 1·415vvw, 1·355vw, 1·340vw, 1·285vw, 1·270vw, 1·240vw, 1·225vw, 1·130vw, 1·100vvw. Prolonged and repeated washing of specimen 2*b* with a large quantity of hot water had no sensible effect on the pattern and only a slight effect on the analysis (Tl_2O, 59·6; Al_2O_3, 19·7; SiO_2, 20·1; total 99·4%), thereby indicating that no appreciable thallous carbonate was present.

Specimen C.—Treatment of products 5*c* or 6*c* with cold 10% nitric acid rendered them almost free from other species and the purified material yielded the following *X*-ray powder data: 5·44ms, 3·65s, 3·37s, 2·89m, 2·41mw, 2·195w, 1·965vw, 1·825w, 1·700w, 1·610vw. Analysis: Tl_2O, 53·7; Al_2O_3, 13·5, SiO_2 32·8; H_2O, negligible; total 100·0 (Calc. for $Tl_2O,Al_2O_3,4SiO_2$: Tl_2O, 55·3; Al_2O_3, 13·3; SiO_2, 31·4%).

Base Exchange of Analcite with Thallium.—The analcite was a synthetic sample prepared by Messrs. I.C.I. Ltd. and kindly supplied by Professor Barrer (Found: Al_2O_3, 23·1; SiO_2, 54·3; H_2O, 7·9. Calc. for $Na_2O,Al_2O_3,4SiO_2,2H_2O$: Al_2O_3, 23·1; SiO_2, 54·6; H_2O, 8·2%). *X*-Ray powder photographs showed 37 arcs in satisfactory agreement with published data (W. H. Taylor, *Z. Krist.*, 1932, **83**, 405). 2 G. of this material were treated with 8 g. of thallous nitrate in a sealed glass tube for 6 days at 250°, after which soluble salts were washed out with hot water, and the residue washed with alcohol and ether (Found: Tl_2O, 53·8; Al_2O_3, 14·2; SiO_2, 31·4; Na_2O, 0·7; H_2O, not determined; total, 100·1%). Optical properties: form unchanged (*i.e.*, isotropic spheroids showing few distinct faces), $n = 1·642$. *X*-Ray powder data: 5·66ms, 3·64s, 3·37s, 2·89m, 2·41mw, 2·20mw, 1·960vw, 1·820w, 1·705w, 1·600vw. Two preparations gave identical optical and *X*-ray data.

Base Exchange of C with Sodium.—Approximately 1 g. of the purified material was subjected to three successive treatments with 20% aqueous sodium nitrate for 2 days at 250°. These extracted approximately 45%, 16%, and 10%, respectively, of the thallium present; total 71%. After the third treatment the refractive indices of the crystals of the washed and dried material tended to a lower limit of 1·485 (refractive index of analcite = 1·486) [Found: Tl_2O, 18·3; Al_2O_3, 17·4; SiO_2, 50·5; Na_2O, 7·3; H_2O (by diff.), 6·5. Calc. for a mixture or solid solution of 67% analcite, 33% C: Tl_2O, 18·2; Al_2O_3, 20·0; SiO_2, 46·9; Na_2O, 9·4; H_2O, 5·5%]. *X*-Ray powder data: 5·72s, 4·90m, 3·65w, 3·45vs, 2·94vs, 2·82vw, 2·72m, 2·54w, 2·42m, 2·24m, 1·91mw, 1·87mw, 1·74m, 1·72vvw, 1·69vw, 1·61w, 1·59w, 1·485vw, 1·480vw, 1·410mw, 1·355mw, 1·305vw, 1·280vw, 1·260vw, 1·215m, 1·175vvw, 1·165vw, 1·015vw, 1·005vw. These are in satisfactory agreement with published data for analcite (W. H. Taylor, *loc. cit.*).

I wish to express my thanks to Professor E. E. Turner, F.R.S., for his interest and encouragement. I am greatly indebted to Professor Barrer, D.Sc., for suggesting the subject of this research, and for much valuable help and advice, in connection with both the experimental work and the writing of this paper. I am grateful also to Drs. F. A. Bannister, M. H. Hey, and V. C. G. Trew for advice, and to the last also for a supply of thallium salts, and to Messrs. I.C.I. Ltd. for the loan of apparatus.

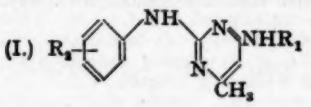
UNIVERSITY OF LONDON (BEDFORD COLLEGE). [*Received, October 30th*, 1948.]

273. *Synthetic Antimalarials. Part XXXVIII.* 2-(6′-*Quinolylguanidino*)-4-β-*diethylaminoethylamino-* and 4-(6′-*quinolylguanidino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidines.*

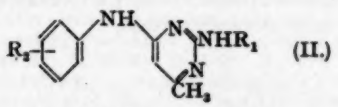
By (the late) J. M. Gulland and P. E. Macey.

Two quinolyl analogues of the phenylguanidinopyrimidines of Parts IV and XXV are prepared by similar methods.

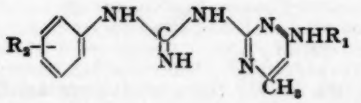
Among the pyrimidine derivatives described in previous parts having significant antimalarial activity are compounds of types (I), (II), (III), and (IV); R_1 = basic alkyl, R_2 = one of many varied substituents and must usually be in the *p*-position.



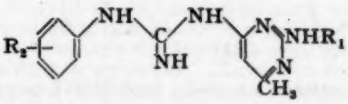
(I.)



(II.)

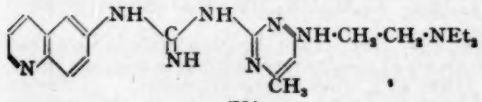


(III.)

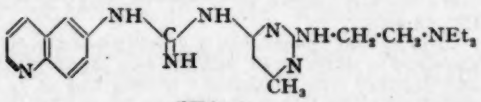


(IV.)

It might be expected that the *p*-substituted phenyl nucleus would be replaceable by a 6′-quinolyl group, to give compounds also of interest from the point of view of providing a link between the older quinoline antimalarials and those of the pyrimidine series. Curd, Graham, Richardson, and Rose (Part XXII, *J.*, 1947, 1613) have shown that this leads to retention of activity in the case of compounds of type (I) but not of type (II), a result which has not so far been explained, although, as the authors point out, it is in line with the case of the 6′-bromo-2-naphthylamino-compounds (Parts V and VI, *J.*, 1946, 366). In general it can be seen that, in active compounds of type (II), R_2 is always a strongly negative substituent such as chloro-, nitro- or cyano-, whereas in type (I) some activity results when R_2 is a group having a positive inductive effect or negative inductive and positive tautomeric effects. If this is significant it may be connected with the presence of a virtual guanidino-group in type (I), in which case the wider range of substituents might be permissible in both classes (III) and (IV).



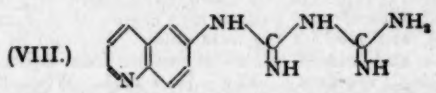
(V.)



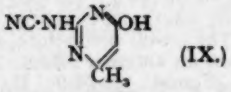
(VI.)

(V) and (VI) were therefore prepared by methods analogous to those used by Curd and Rose (Part IV, *J.*, 1946, 362) and Crowther, Curd, and Rose (Part XXV, *J.*, 1948, 586).

In the former case 6-aminoquinoline (VII) (Knueppel, *Annalen*, 1900, **310**, 84) reacted readily with dicyandiamide in hydrochloric acid to yield 6-diguanidoquinoline (VIII) which condensed with ethyl acetoacetate in sodium hydroxide solution giving 2-(6′-quinolylguanidino)-



(VIII.)



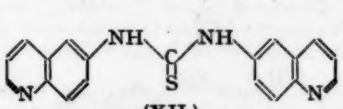
(IX.)

4-hydroxy-6-methylpyrimidine, an identical specimen of which was prepared by interaction of (VII) and 2-cyanamino-4-hydroxy-6-methylpyrimidine (IX) (Pohl, *J. pr. Chem.*, 1908, **77**, 533). This reacted successively with phosphoryl chloride and β-diethylaminoethylamine to yield (V).

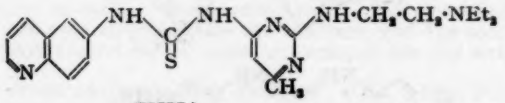
In the latter case 6-guanidinoquinoline was prepared from (VII) and cyanamide *via* the nitrate, but the yield was low and the product was difficult to obtain free from an unidentified red impurity. Reaction of (VII) with *S*-methyl*iso*thiouronium sulphate (Arndt, *Ber.*, 1921, **54**, 2236) gave a 50—60% yield of 6-guanidinoquinoline sulphate which was converted quantitatively into the free base. Attempts to condense this with 2-hydroxy-4-methylthio-6-methylpyrimidine (X) (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 431) or 2-β-diethyl-

aminoethylamino-4-ethylthio-6-methylpyrimidine, prepared from sodium ethyl sulphide and 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (Part VI, *J.*, 1946, 370), were unsuccessful under various conditions. This work was done before the publication of Part XXV, in which Crowther, Curd, and Rose report that the condensation of *p*-chlorophenylguanidine with (X) required 48 hours in boiling *o*-dichlorobenzene, conditions more vigorous than were used here.

A much more satisfactory route to (VI) proved to be *via* 6-*iso*thiocyanatoquinoline (XI), which was prepared from (VII) and thiocarbonyl chloride after unsuccessful attempts from carbon disulphide. Under certain conditions (VII) and thiocarbonyl chloride yielded mainly the diquinolyl thiourea (XII), as found by Schönhöfer and Henecka (G.P. 583,207); this also resulted from the interaction of (VII) and (XI). (XI) reacted readily with 4-amino-2-β-diethylaminoethylamino-6-methylpyrimidine (Hull, Lovell, Openshaw, and Todd, Part XI, *J.*, 1947, 41), and the resultant thiourea (XIII) was converted into the guanidine (VI) by means of ammonia and mercuric oxide.



(XII.)



(XIII.)

Compounds (V), (VI), and (VII) were tested by Dr. D. G. Davey, of Imperial Chemical Industries Ltd. against *P. gallinaceum*.

Experimental.

6-Diguanidoquinoline Hydrochloride.—6-Aminoquinoline (8·0 g.), dicyandiamide (5·5 g.), concentrated hydrochloric acid (12·0 g.), and water (44 c.c.) were heated at 100° under reflux for 10½ hours, neutralised with concentrated ammonia solution and cooled. The *product* which separated recrystallised from water in colourless prisms, m. p. 258° (4·5 g.) (Found: C, 50·0; H, 5·2; N, 31·5. $C_{11}H_{12}N_6$,HCl requires C, 49·9; H, 4·95; N, 31·8%). It formed an alkaline solution in water. The *base* was precipitated by adding 5N-sodium hydroxide, and formed colourless plates from water, m. p. 165° (Found: C, 58·0; H, 5·4; N, 36·0. $C_{11}H_{12}N_6$ requires C, 57·9; H, 5·3; N, 36·8%).

2-(6′-Quinolylguanidino)-4-hydroxy-6-methylpyrimidine Dihydrochloride.—6-Aminoquinoline (15 g.), 2-cyanamino-4-hydroxy-6-methylpyrimidine (16 g.), concentrated hydrochloric acid (22·5 g.), and water (55 c.c.) were heated at 100° for 10½ hours. The yellow solution was cooled to 0° and treated with concentrated hydrochloric acid (36 c.c.) to complete precipitation of the *hydrochloride*. This dissolved in water at 40°, and, when the solution was made 10% with respect to hydrochloric acid, separated as fine colourless needles, m. p. 242° (Found: N, 22·0; Cl′, 18·7. $C_{15}H_{14}ON_6$,2HCl,H_2O requires N, 21·8; Cl′, 18·4%).

2-(6′-Quinolylguanidino)-4-hydroxy-6-methylpyrimidine.—(*a*) The crude hydrochloride above was dissolved in water at 40° and the *base* precipitated with excess of concentrated ammonia solution, dried, and digested with methanol; it then had m. p. 275° (yield 37% from 6-aminoquinoline). It formed colourless plates from nitrobenzene, m. p. 275° (Found: C, 61·0; H, 5·0; N, 28·6. $C_{15}H_{14}ON_6$ requires C, 61·2; H, 4·8; N, 28·6%).

(*b*) 6-Diguanidoquinoline hydrochloride (2·5 g.) and sodium hydroxide (0·7 g.) were dissolved in warm 92% ethanol (16 c.c.). Ethyl acetoacetate (3·0 c.c.) was added, and the solution left for 24 hours; it had then solidified to a white mass. After being washed with ethanol and water and digested with methanol it had m. p. 278°, not depressed by mixture with (*a*).

4-Chloro-2-(6′-quinolylguanidino)-6-methylpyrimidine.—2-(6′-Quinolylguanidino)-4-hydroxy-6-methylpyrimidine (11 g.) and phosphoryl chloride (22 c.c.) were heated under reflux in an oil-bath at 120—130° for 45 minutes to give a golden oil. This was poured on crushed ice (300 g.) containing sodium hydroxide (44 g.), the pale salmon-coloured precipitate was dissolved in warm 10% hydrochloric acid, and the solution was stirred with charcoal, filtered, and poured into excess of sodium hydroxide solution. The cream precipitate, roughly dried, was used for the next stage. It could be purified by passing down an alumina column in chloroform, and formed colourless needles from aqueous ethanol, m. p. 208° (Found: C, 58·0; H, 4·1. $C_{15}H_{13}N_6Cl$ requires C, 57·6; H, 4·2%). When the reaction mixture was poured on ice with no sodium hydroxide, the *hydrochloride* was obtained. This formed fine colourless needles from water on addition of hydrochloric acid (Found: C, 46·8; H, 4·3; Cl′, 18·0. $C_{15}H_{13}N_6Cl$,2HCl requires C, 46·7; H, 3·9; Cl′, 18·4%).

2-(6′-Quinolylguanidino)-4-β-diethylaminoethylamino-6-methylpyrimidine.—4-Chloro-2-(6′-quinolylguanidino)-6-methylpyrimidine (above yield), β-diethylaminoethylamine (6·0 g.), chlorobenzene (40 c.c.), sodium hydroxide (6·0 g.), and water (40 c.c.) were stirred and boiled under reflux for 45 minutes. The chlorobenzene and the excess of amine were removed in steam, and the brownish solid was collected and dissolved in N-acetic acid, and the solution was warmed with decolourising charcoal, filtered, and poured into iced sodium hydroxide solution. The precipitated cream solid became brown and sticky when collected. It was dried and extracted in a Soxhlet apparatus with ethyl acetate from which it formed colourless prisms, m. p. 196—197° (3·8 g.). The *product* recrystallised from acetone in colourless prisms, m. p. 197° (Found: C, 64·3; H, 7·0; N, 28·5. $C_{21}H_{28}N_8$ requires C, 64·2; H, 7·2; N, 28·6%).

2-β-Diethylaminoethylamino-4-ethylthio-6-methylpyrimidine.—Sodium (0·8 g.) was dissolved in

absolute ethanol (45 c.c.) and ethylthiol (2·5 c.c.) added, followed by 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (7·5 g.). The solution was refluxed for 1 hour, the solvent evaporated, water (80 c.c.) added, and the oil extracted with benzene, which was distilled off to leave a golden oil (8·1 g.). When cooled in solid carbon dioxide this crystallised but melted again at 16°. With excess of picric acid in ethanol, it formed a *picrate* which gave yellow prisms from ethanol, m. p. 158° (Found: S, 4·1. $C_{13}H_{24}N_4S,2C_6H_3O_7N_3$ requires S, 4·4%). Distillation in a vacuum yielded the pure *base* as a colourless oil which crystallised on standing; b. p. 105—115°/0·04 mm., m. p. 24° (Found: N, 20·9; S, 11·7. $C_{13}H_{24}N_4S$ requires N, 20·9; S, 11·9%).

6-*Guanidinoquinoline Sulphate*.—*S*-Methyl*iso*thiouronium sulphate (5·2 g.) and 6-aminoquincline (26 g.) were heated in an oil-bath at 160—180° for 2 hours. The cooled mass was digested with ethanol, and the light-brown solid collected, washed with ethanol and ether, and crystallised from water (500 c.c.) with a little decolourising charcoal. The *product* formed colourless, alum-shaped crystals from water, m. p. 302° (5·3 g.) (Found: SO_4'', 20·3. $C_{10}H_{10}N_4,\frac{1}{2}H_2SO_4$ requires SO_4'', 20·4%). The excess of amine could be recovered by precipitating the hydrochloride from the ethanol with concentrated hydrochloric acid.

6-*Guanidinoquinoline*.—(*a*) 6-Guanidinoquinolinium sulphate (5·9 g.) was triturated with 8% sodium hydroxide solution (80 c.c.) and the mixture of oil and water extracted continuously and exhaustively with ether. Evaporation of the solvent yielded the theoretical amount of the *base* which crystallised from acetone as colourless prisms, m. p. 175—176° (Found: C, 63·8; H, 5·0; N, 30·1. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1%). (*b*) 6-Aminoquinoline (7·5 g.) and cyanamide (7·4 g.) were melted on a water-bath and then cooled. Concentrated hydrochloric acid (24 c.c.) was added down a funnel dipping below the surface and caused a violent reaction. When this had subsided 2N-nitric acid (50 c.c.) was added, and the solution, cooled in an ice-box, slowly deposited an orange-coloured solid (9·5 g.). This was dissolved in warm water, cooled somewhat, filtered free from the red solid which separated initially, cooled further, and scratched; light orange-coloured crystals then separated. These were recrystallised from water with decolourising charcoal and a little nitric acid as almost colourless long prisms, m. p. 185° (decomp.). Treated with 8% sodium hydroxide solution and extracted continuously with ether this yielded 6-guanidinoquinoline, m. p. 173° not depressed by mixture with specimen from (*a*). Heated with 1 molecular proportion of 2-β-diethylaminoethylamino-4-ethylthio-6-methylpyrimidine or 2-hydroxy-4-methylthio-6-methylpyrimidine for various times up to 12 hours and at temperatures up to 180°, 6-guanidinoquinoline caused the evolution of alkylthiol, but in all cases sulphur-containing mixtures were obtained and crystalline products could not be isolated.

6-iso*Thiocyanatoquinoline*.—Thiocarbonyl chloride (2·1 c.c.) was added in one portion to a vigorously stirred solution of 6-aminoquinoline (3·0 g.) in concentrated hydrochloric acid (1·8 c.c.) and water (35 c.c.). After 1½ hours, by which time the smell of thiocarbonyl chloride had ceased, the yellow precipitate was filtered off and washed with water, in which it partly dissolved, and the filtrate and washings were poured into excess of iced sodium hydroxide solution. The white precipitate was collected, washed with sodium hydroxide solution and water, dried, and extracted exhaustively with light petroleum (b. p. 40—60°) in a Soxhlet apparatus. 6-iso*Thiocyanatoquinoline*, m. p. 94° (2·8 g.), separated from the extract. It formed colourless needles, m. p. 94°, when a solution in pyridine was diluted and cooled (Found: N, 14·8; S, 17·6. $C_{10}H_6N_2S$ requires N, 15·0; S, 17·2%).

NN′-*Di*-6′-*quinolylthiourea*.—6-*iso*Thiocyanatoquinoline was melted with 6-aminoquinoline (1 mol.) in a water-bath. The melt hardened to a white solid, m. p. 197°, which formed colourless prisms from methanol, m. p. 198° (Schönhöfer and Henecka, G.P. 583,207, give m. p. 199°; Haskelberg, *J. Org. Chem.*, 1947, **12**, 434, gives m. p. 217°) (Found: N, 16·7; S, 9·9. Calc. for $C_{19}H_8N_4S$: N, 17·0; S, 9·7%).

4-(6′-*Quinolylthioureido*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine*.—4-Amino-2-β-diethylaminoethylamino-6-methylpyrimidine (3 g.) and 6-*iso*thiocyanatoquinoline (3 g.) were melted and heated on a water-bath for ½ hour. The resulting pale yellow solid was ground with benzene and heated again for ½ hour after all the solvent had evaporated, then ground with more benzene, and collected; it then had m. p. 171° (4·7 g.). The *product* formed a mass of colourless needles from ethanol, m. p. 179—180° (Found: N, 23·6; S, 7·9. $C_{21}H_{27}N_7S$ requires N, 24·0; S, 7·8%).

4-(6′-*Quinolylguanidino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine*.—4-(6′-Quinolylthioureido)-2-β-diethylaminoethylamino-6-methylpyrimidine (2·0 g.), dissolved in 12% (w/v) methanolic ammonia (60 c.c.), was stirred with yellow mercuric oxide (2·0 g.) for 4 hours at 35—40° under reflux. The black suspension was cooled and stirred with excess of dilute hydrochloric acid, and the rest of the mercury precipitated with sodium sulphide. The mercuric sulphide was filtered off, the cloudy filtrate centrifuged, and the centrifugate poured into excess of 2N-sodium hydroxide. The white solid precipitated (1·8 g., m. p. 193—194°) crystallised from 95% acetone as long colourless prisms, m. p. 200° (1·2 g.). Recrystallisation from benzene or 97% acetone then gave long colourless prisms, m. p. 198° (Found: C, 64·2; H, 6·9; N, 28·5. $C_{21}H_{25}N_8$ requires C, 64·2; H, 7·2; N, 28·6%).

The authors thank the Medical Research Council for a grant to one of them (P. E. M.).

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, September 14th*, 1948.]

274. *Synthetic Antimalarials. Part XXXIX. Dialkylaminoalkylaminoquinoxalines.*

By A. F. Crowther, (the late) F. H. S. Curd, D. G. Davey, and G. J. Stacey.

Following the observation that 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline (Part XXVII, *J.*, 1948, 777) possessed marked activity against avian malaria (*P. gallinaceum* in chicks), it is shown that increasing the complexity of the side-chain has a dystherapeutic effect, whilst removing the 2-chlorine atom, or replacing it by other groups such as hydroxyl, ethoxyl, or thiol, leads to a loss of activity. In the simple 2-chloro-3-dialkylaminoalkylaminoquinoxalines, replacing the chlorine by methyl has a similar effect.

Although in the majority of cases only one product appears to be formed from 2 : 3 : 6-trichloroquinoxaline and a dialkylaminoalkylamine, with γ-piperidinopropylamine 2 : 7-*dichloro*-3-γ-*piperidinopropylaminoquinoxaline* was also isolated. Parallel proof that the main product was the 2 : 6-*dichloro*-analogue validates the assumption made in Part XXVII that in 2 : 3 : 6-trichloroquinoxaline the chlorine atom in the 3-position is more reactive than that in the 2-position, and provides evidence for the structure of all the compounds of type (I) described in this paper. An indication of initial reaction at both the 2- and the 3-position was also obtained in the condensation of (VII; R = H, R′ = R″ = Cl) with β-dimethylaminoethylamine. Reaction in the cold led to the isolation of 2 : 6-*dichloro*-3-β-*dimethylaminoethylaminoquinoxaline* which was readily cyclised by heat to give 6-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene*, whilst in boiling alcohol the 7-*chloro*-isomer of the latter was also formed.

2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline was hydrolysed to give 6-*chloro*-3-γ-*piperidinopropylamino*-2-*hydroxyquinoxaline*, but attempts to synthesis the hydroxy-compound from N-(4-*chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* failed. Cyclisation to a quinoxaline derivative could be accomplished only with simultaneous loss of the γ-piperidinopropylamino-side-chain; cyclisation by heat gave 5(or 6)-*chlorobenziminazole*-2-*carboxy*-γ-*piperidinopropylamide*.

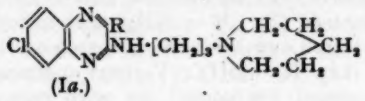
In Part XXVII (Haworth and Robinson, *J.*, 1948, 777) the preparation of a number of dialkylaminoalkylaminoquinoxalines was reported. The observation that 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline (I; R = Cl, R′ = $[CH_2]_2$·NEt_2) was active against the blood forms of *P. gallinaceum* in chicks at a dose of 10 mg./kg. made it of interest to examine further compounds of this type and also strictly to establish the constitution of the products. For the latter purpose it was decided to employ compounds containing the γ-piperidinopropylamino-side-chain since other work suggested that these were likely to be the most readily crystallised.

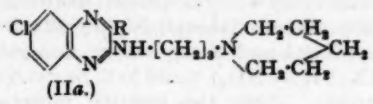
When equimolecular proportions of 2 : 3 : 6-trichloroquinoxaline and γ-piperidinopropylamine reacted in boiling alcoholic solution, formation of two products, 2 : 6- (I*a*; R = Cl), m. p. 108°, and 2 : 7-*dichloro*-3-γ-*piperidinopropylaminoquinoxaline* (II*a*; R = Cl), m. p. 76—77°, in the approximate ratio of 3 : 1, was observed. The orientations of these two isomers were proved by reductive partial dehalogenation, using hydrogen and Raney nickel, to give, respectively, 7- (I*a*; R = H) and 6-*chloro*-2-γ-*piperidinopropylaminoquinoxaline* (II*a*; R = H), both of which were prepared by the independent unambiguous syntheses described below, in which the earlier stages were analogous to methods previously reported in the literature for related compounds (cf. Plöchl, *Ber.*, 1886, **19**, 7; Hinsberg, *Annalen*, 1888, **248**, 73; *Ber.*, 1892, **25**, 2417; *ibid.*, 1908, **41**, 2032; F.P. 824,531, *Chem. Zentr.*, 1938, II, 178; Motylewski, *Ber.*, 1908, **41**, 802).

4-Chloro-2-nitroaniline was heated with bromoacetic acid to give N-(4-*chloro*-2-*nitrophenyl*)-*glycine* (IV; R = Cl, R′ = R″ = H), which on reduction with hydrogen and Raney nickel afforded 7-*chloro*-2-*hydroxy*-3 : 4-*dihydroquinoxaline* (V; R = Cl, R′ = H). Oxidation of this compound with ammoniacal silver nitrate gave 7-*chloro*-2-*hydroxyquinoxaline* (VI; R = Cl, R′ = R″ = H), converted by phosphoryl chloride into 2 : 7-*dichloroquinoxaline* (VII; R = Cl, R′ = R″ = H) and thence by γ-piperidinopropylamine into (I*a*; R = H). The identity of the 7-chloro-2-γ-piperidinopropylaminoquinoxaline prepared in this way with the material obtained from 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline was established by comparison not only of the bases, but also of the *picrates*.

The starting material for the synthesis of the isomeric 6-chloro-2-γ-piperidinopropylaminoquinoxaline was 4-chloro-1 : 2-dinitrobenzene. This reacted smoothly in benzene solution with ethyl aminoacetate to give *ethyl* 5-*chloro*-2-*nitroanilinoacetate* (IV; R = H, R′ = Cl, R″ = Et) (cf. the reaction with ammonia to give 5-chloro-2-nitroaniline, Laubenheimer, *Ber.*, 1876, **9**, 1826) which, on catalytic reduction and simultaneous ring-closure, gave 6-*chloro*-2-*hydroxy*-3 : 4-*dihydroquinoxaline* (V; R = H, R′ = Cl). This was then successively converted into the analogous *compounds* (VI) and (VII), and thence into 6-chloro-2-γ-piperidinopropylamino-

quinoxaline (II*a*; R = H), identical in every way with the partial-dehalogenation product of 2 : 7-dichloro-3-γ-piperidinopropylaminoquinoxaline.


(I*a*.)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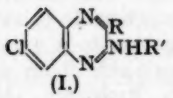
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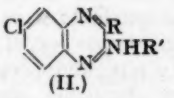
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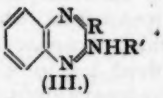
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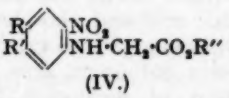
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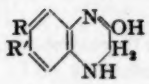
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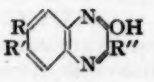
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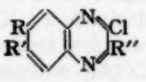
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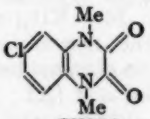
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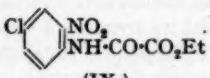
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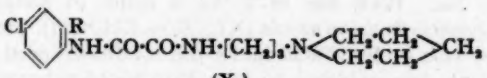
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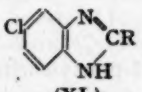
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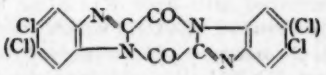
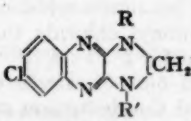
(XII.) 


(XIII.)

The degradation of (I*a*; R = Cl) to 7-chloro-2-γ-piperidinopropylaminoquinoxaline was also effected by a two-step process in which it was first treated with sodium hydrogen sulphide in alcohol, to give *6-chloro-3-γ-piperidinopropylamino-2-mercaptoquinoxaline* (I*a*; R = SH), and this was then desulphurised by means of Raney nickel. However, application of this method to 2 : 7-dichloro-3-γ-piperidinopropylaminoquinoxaline failed, for, although conversion into *7-chloro-3-γ-piperidinopropylamino-2-mercaptoquinoxaline* (II*a*; R = SH) was successful, subsequent treatment with Raney nickel gave only intractable material. Early attempts to reduce 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline catalytically to (I*a*; R = H) with the addition of one equivalent of sodium hydroxide as acid-binding agent (cf. Whitmore and Revukas, *J. Amer. Chem. Soc.*, 1940, **62**, 1691; Krahler and Burger, *ibid.*, 1941, **63**, 2370) led to mixtures, from which the only isolable product was *6-chloro-3-γ-piperidinopropylamino-2-ethoxyquinoxaline* (I*a*; R = OEt) identical with material made by the action of alcoholic sodium ethoxide on (I*a*; R = Cl) (cf. the observations of Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405, in the quinazoline series).

Earlier, an abortive attempt was made to establish the orientation of the major product of interaction of 2 : 3 : 6-trichloroquinoxaline and γ-piperidinopropylamine (2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline) by an independent synthesis of *6-chloro-3-γ-piperidinopropylamino-2-hydroxyquinoxaline* (I*a*; R = OH) obtained from it by short acid hydrolysis; prolonged hydrolysis led to 6-chloro-2 : 3-dihydroxyquinoxaline (VI; R = Cl, R′ = H, R″ = OH), characterised by conversion into *6-chloro-2 : 3-diketo-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline* (VIII) identical with material made from authentic (VI; R = Cl, R′ = H, R″ = OH), and distinct from *6-chloro-2 : 3-dimethoxyquinoxaline*.

4-Chloro-2-nitroaniline was caused to interact with a large excess of ethyl oxalate to give *ethyl 4-chloro-2-nitro-oxanilate* (IX) together with a smaller proportion of *NN′-di-(4-chloro-2-nitrophenyl)oxamide*. (IX) was readily hydrolysed to 4-chloro-2-nitroaniline by cold, dilute, aqueous sodium hydroxide, and this ease of hydrolysis was reflected in the difficulties at first encountered in the preparation of *N-(4-chloro-2-nitrophenyl)-N′-(γ-piperidinopropyl)oxamide* (X; R = NO_2) from (IX) and γ-piperidinopropylamine. For example, treatment of (IX) with excess of γ-piperidinopropylamine alone, with or without external heating, gave exclusively 4-chloro-2-nitroaniline and *NN′-di-(γ-piperidinopropyl)oxamide*, independently prepared from γ-piperidinopropylamine and ethyl oxalate. In this connexion it is also noteworthy that *NN′*-di-(4-chloro-2-nitrophenyl)oxamide, when stirred with excess of γ-piperidinopropylamine in the cold, was converted almost quantitatively into 4-chloro-2-

nitroaniline and *NN'*-di-(γ-piperidinopropyl)oxamide. The desired mixed oxamide (X; R = NO_2) was ultimately obtained by causing equimolecular quantities of γ-piperidinopropylamine and ethyl 4-chloro-2-nitro-oxanilate to react in cold benzene solution, and its reduction to N-(*4-chloro-2-aminophenyl*)-N'-(*γ-piperidinopropyl*)*oxamide* (X; R = NH_2) was accomplished with hydrogen and Raney-nickel catalyst. The projected synthesis was arrested at this stage since (X; R = NH_2) could not be cyclised to give (I*a*; R = OH). Various cyclising agents were tried: either the starting material was recovered unchanged (as with concentrated sulphuric acid and phosphorus pentoxide), or the products were unrecognisable (phosphorus pentachloride, phosphoryl chloride, phosphorus trichloride) or, if cyclisation to a quinoxaline derivative did occur, this involved loss of the γ-piperidinopropylamino-side-chain and the formation of 6-chloro-2 : 3-dihydroxyquinoxaline (aqueous alcoholic hydrogen chloride). When (X; R = NH_2) was heated at 190—200°, cyclisation with loss of water occurred, but to give the benziminazole derivative (XI; R = $CO{\cdot}NH{\cdot}[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$). The constitution of this substance was first indicated by its degradation to 5(or 6)-*chlorobenziminazole-2-carboxylic acid* (XI; R = CO_2H) and thence to 5(or 6)-chlorobenziminazole (XI; R = H) identical with material made by the method of Fischer (*Ber.*, 1904, **37**, 556); substantiating proof was provided by its synthesis by a method analogous to that described by Copeland and Day (*J. Amer. Chem Soc.*, 1943, **65**, 1072) for a series of benziminazole-2-carboxyamides. 5(or 6)-*Chloro-2-hydroxymethylbenziminazole* (XI; R = $CH_2{\cdot}OH$), prepared by treating 4-chloro-1 : 2-phenylenediamine with glycollic acid under the conditions used by Phillips (*J.*, 1928, 2395) for similar condensations, was oxidised to give 5(or 6)-chlorobenziminazole-2-carboxylic acid (cf. the synthesis of benziminazole-2-carboxylic acid by Bistrzycki and Przeworski, *Ber.*, 1912, **45**, 3489). With thionyl chloride this was converted into 5'(or 6') : 5''(or 6'')-*dichloro*-3 : 6-*diketodibenziminazolo*(1' : 2' : 1 : 2)(1'' : 2'' : 4 : 5)*piperazine* (XII), which with γ-piperidinopropylamine yielded 5(or 6)-*chlorobenziminazole-2-carboxy-γ-piperidinopropylamide*.

Having confirmed the deduction made in Part XXVII (*loc. cit.*) that the chlorine atom in the 3-position of 2 : 3 : 6-trichloroquinoxaline was more reactive than that in the 2-position, we prepared further compounds of type (I; R = Cl, R' = dialkylaminoalkyl). Originally the reaction between 2 : 3 : 6-trichloroquinoxaline and β-diethylaminoethylamine (2 mols.) was carried out by mixing them at 0°, and evidence was adduced to show that an uncontrolled reaction led to the production of some 6-chloro-2 : 3-bis-(β-diethylaminoethylamino)quinoxaline. When this method was tried with γ-diethylaminopropylamine and more complex aminoalkylamines, very little reaction occurred, and after considerable experimentation it was found that the use of equimolecular proportions of the reactants in boiling alcohol gave the best results. In this way 2 : 6-dichloroquinoxaline *derivatives* (I; R = Cl) were made in which R' was 3-*γ-diethylaminopropyl*, 3-*δ-diethylamino-α-methylbutyl* and 3-*γ*-di-*n*-butylaminopropyl. In the last case the *hydrochloride* was separated directly from the reaction mixture, and no isomeric product was sought. In the other two cases failure to detect any of the second isomer was possibly due to its loss during crystallisation; alternatively, it may have been attributable to hydrolysis during the working-up process, in the course of which the product was extracted with hydrochloric acid. In support of the latter hypothesis, it can be said that in preliminary condensations of 2 : 3 : 6-trichloroquinoxaline with γ-piperidinopropylamine, involving extraction with hydrochloric acid, only 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline was isolated, and that the second isomer was detected only when acetic acid was used in place of hydrochloric acid.

In order to obtain 2 : 6-*dichloro*-3-β-*dimethylaminoethylaminoquinoxaline* (I; R = Cl, R' = $[CH_2]_2{\cdot}NMe_2$) it was essential to carry out the reaction between 2 : 3 : 6-trichloroquinoxaline and β-dimethylaminoethylamine in the cold. In boiling alcoholic solution loss of methyl chloride occurred in addition to condensation, and the formation of two isomeric tricyclic compounds, 6-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (XIII; R = Me, R' = H, *n* = 2) and 7-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (XIII; R = H, R' = Me, *n* = 2) was observed. As expected, the former was formed in greater quantity, but it was not possible completely to free it from the latter although a pure specimen was obtained by heat-cyclisation of 2 : 6-dichloro-3-β-dimethylaminoethylaminoquinoxaline, and the substantial identity of the two products was demonstrated by the formation of identical *acetyl* and *benzoyl* derivatives. Heating (I; R = Cl, R' = $[CH_2]_2{\cdot}NMe_2$) at 135—145° gave not only 6-chloro-1-methyl-1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene itself, but also a derived *dimethochloride*, approximately 56% of the methyl chloride being retained in this manner.

2 : 3 : 6-Trichloroquinoxaline and *NN'*-dimethylethylenediamine in boiling alcohol gave

rise to *6-chloro-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene* (XIII; R = R′ = Me, *n* = 2), but the only product isolated from the reaction of (VII; R = H, R′ = R″ = Cl) and ethylenediamine under similar conditions was *NN′-bis-(2 : 6-dichloro-3-quinoxalyl)ethylenediamine* [cf. the condensation of 2 : 3-dichloroquinoxaline with ethylenediamine to give 1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene (Ogg and Bergström, *J. Amer. Chem. Soc.*, 1931, **53**, 1847)].

Antimalarial Activities.

The compounds were tested for antimalarial activity against the blood forms of *P. gallinaceum* in chicks, by the method previously described (Davey, *Ann. Trop. Med. Parasit.*, 1946, **40**, 52). The results given below are expressed in the same way as in previous papers in this series (*J.*, 1946, 343).

Ref. no.	Compound	Dose, mg./kg.	Activity
6971	2 : 6-Dichloro-3-β-dimethylaminoethylaminoquinoxaline	80	++
		40	+
		20	−
5587	2 : 6-Dichloro-3-β-diethylaminoethylaminoquinoxaline *	20	++
		10	+
		5	−
6231	2 : 6-Dichloro-3-γ-diethylaminopropylaminoquinoxaline	40	++
		20	+
6219	2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline	80	++
		40	+
		20	−
6396	2 : 6-Dichloro-3-γ-di-*n*-butylaminopropylaminoquinoxaline hydrochloride	160	+ to ++
		80	+
		40	−
6480	2 : 6-Dichloro-3-δ-diethylamino-α-methylbutylaminoquinoxaline	160	++
		80	+
		40	±
		20	−
6991	2 : 7-Dichloro-3-γ-piperidinopropylaminoquinoxaline	160	+
		80	−
7219	6-Chloro-3-γ-piperidinopropylamino-2-hydroxyquinoxaline	80	−
6946	6-Chloro-3-γ-piperidinopropylamino-2-ethoxyquinoxaline	160	−
7175	6-Chloro-3-γ-piperidinopropylamino-2-thiolquinoxaline	160	−
6860	7-Chloro-2-β-diethylaminoethylaminoquinoxaline hydrochloride	160	−
6990	7-Chloro-2-γ-diethylaminopropylaminoquinoxaline hydrochloride	160	−
6736	7-Chloro-2-γ-piperidinopropylaminoquinoxaline hydrochloride	160	−
7109	6-Chloro-2-β-diethylaminoethylaminoquinoxaline	80	−
7034	6-Chloro-2-γ-piperidinopropylaminoquinoxaline	160	−
7318	2-Chloro-3-β-diethylaminoethylaminoquinoxaline *	80	+
		40	−
5987	2-Chloro-3-γ-diethylaminopropylaminoquinoxaline *	80	+
7216	2-β-Diethylaminoethylaminoquinoxaline	80	−
7215	2-γ-Diethylaminopropylaminoquinoxaline	80	−
7214	2 β-Diethylaminoethylamino-3-methylquinoxaline	80	−
7221	2-γ-Diethylaminopropylamino-3-methylquinoxaline	80	−
7310	2-β-Diethylaminoethylamino-3-hydroxyquinoxaline	160	−
7173	2-γ-Piperidinopropylamino-3-hydroxyquinoxaline	160	−
6479	*NN′*-Bis-(2 : 6-dichloro-3-quinoxalyl)ethylenediamine	80	−
7085	6-Chloro-1-ethyl-1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene *	160	−
6599	6-Chloro-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene	160	−
6730	6-Chloro-1′-ethyl-1′ : 5′-diaza-2 : 3-pentamethylenequinoxaline	160	−

* Described in Part XXVII (*loc. cit.*) and included for comparison, or only subsequently tested.

The following compounds were also tested for prophylactic activity against *P. gallinaceum* in chicks by the method described elsewhere (Davey, *Ann. Trop. Med. Parasit.*, 1946, **40**, 453) but none showed activity: 5587 and 6736 at 160 mg./kg., 6219, 6479, 6480, 6730, 6860, 6946, 6991, 7034, 7085, 7109, 7215, 7216, 7219, 7221, and 7318 at 80 mg./kg., and 7214 at 40 mg./kg.

In Part XXVII (*loc. cit.*) the cyclisation of (I; R = Cl, R′ = $[CH_2]_2$·NEt_2) to give (XIII; R = Et, R′ = H, *n* = 2) was reported. This compound has been prepared again, for test as an antimalarial, together with the corresponding cyclisation product from (I; R = Cl, R′ = $[CH_2]_3$·NEt_2), namely *6-chloro-1′-ethyl-1′ : 5′-diaza-2 : 3-pentamethylenequinoxaline* (XIII; R = Et, R′ = H, *n* = 3). The results of these tests against *P. gallinaceum* in chicks are shown in the Table in comparison with those of the corresponding compounds of type (I).

The inactivity of the former renders it unlikely that the activity of the 2 : 6-dichloro-3-dialkylaminoalkylaminoquinoxalines has any connection with their capacity to undergo cyclisation (which might have occurred *in vivo*), and this conclusion is supported by the activity of (I*a*; R = Cl) which is incapable of such a transformation.

The synthesis of 2 : 6- and 2 : 7-dichloroquinoxaline mentioned above permitted the preparation of a number of 6- and 7-chloro-2-dialkylaminoalkylaminoquinoxalines of types (II and I; R = H) in addition to the γ-piperidinopropylamino-derivatives already referred to. The results of antimalarial tests on these compounds (described in the experimental section) are given in the Table. Their uniform inactivity, in contrast to the activity of the compounds of types (I and II; R = Cl), clearly indicated the importance of the 2-chlorine atom, and this was also demonstrated by the inactivity of 2-β-*diethylaminoethylaminoquinoxaline* (III; R = H, R′ = $[CH_2]_2$·NEt_2) and of the corresponding γ-*diethylaminopropylamino*-derivative (III; R = H, R′ = $[CH_2]_3$·NEt_2) which bear a similar relation to the slightly active 2-chloro-3-β-diethylaminoethylamino- and 2-chloro-3-γ-diethylaminopropylamino-quinoxaline (III; R = Cl, R′ = $[CH_2]_2$·NEt_2 and $[CH_2]_3$·NEt_2, respectively) described in Part XXVII. A methyl group in place of the chlorine atom in these last two compounds was incapable of conferring activity; 2-β-*diethylaminoethylamino-3-methylquinoxaline* (III; R = Me, R′ = $[CH_2]_2$·NEt_2) and 2-γ-*diethylaminopropylamino-3-methylquinoxaline* (III; R = Me, R′ = $[CH_2]_3$·NEt_2) were inactive at doses of 80 mg./kg. The condensation of 2-chloro-, 2-chloro-3-methyl-, 2 : 6-dichloro-, and 2 : 7-dichloro-quinoxaline with dialkylaminoalkylamines was carried out by heating with a large excess of the amine under reflux.

The non-equivalence of a methyl group and a chlorine atom for the display of antimalarial activity suggested that a reactive chlorine atom might be required in order to undergo hydrolysis *in vivo* to give the corresponding hydroxy-compound as the actual antimalarial substance. 6-Chloro-3-γ-piperidinopropylamino-2-hydroxyquinoxaline and some other compounds of a similar type were therefore tested, but none showed antimalarial activity. This series included 2-β-*diethylaminoethylamino-3-hydroxyquinoxaline* (III; R = OH, R′ = $[CH_2]_2$·NEt_2), prepared by hydrolysis of (III; R = Cl, R′ = $[CH_2]_2$·NEt_2), and 2-γ-*piperidinopropylamino-3-hydroxyquinoxaline* (III; R = OH, R′ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2) which was formed during a preparation of 2-*chloro-3-γ-piperidinopropylaminoquinoxaline* (III; R = Cl, R′ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2) in which the product was extracted with hot dilute hydrochloric acid.

Although the above work clearly demonstrated a difference in reactivity between the chlorine atoms in the 2- and 3-positions of 2 : 3 : 6-trichloroquinoxaline, all attempts to effect selective hydrolysis failed. With boiling 5N-hydrochloric acid the trichloro-compound was slowly hydrolysed to 6-chloro-2 : 3-dihydroxyquinoxaline, and with weaker acid only the same substance and unchanged material were isolated; it was unchanged by 2N-sodium hydroxide at room temperature, in contrast to the behaviour of 2 : 4-dichloroquinazoline which was hydrolysed to 2-chloro-4-hydroxyquinazoline by this treatment (Part XIV, Curd, Landquist, and Rose, *J.*, 1947, 775).

Experimental.

N-(4-Chloro-2-nitrophenyl)glycine (IV; R = Cl, R′ = R″ = H).—4-Chloro-2-nitroaniline (172·5 g.) and bromoacetic acid (139 g.) were stirred together at 125—130° for 1 hour under reflux, with a vigorous stream of air passing through the mixture to remove hydrogen bromide. The mixture was then cooled and extracted with hot water (500 c.c.) and sufficient ammonia to make the solution alkaline to brilliant-yellow. The filtered extract deposited the ammonium salt of the product on cooling. This was collected and the filtrate used for re-extraction of the reaction mixture, the process being repeated four times. The combined crops of ammonium salt were suspended in the final filtrates, and the mixture acidified hot with hydrochloric acid. The precipitated product was collected, washed with water, and dried (yield, 104 g.). Crystallisation from alcohol gave *N-(4-chloro-2-nitrophenyl)glycine* as golden yellow prisms, m. p. 194° (decomp.) (Found: C, 41·8; H, 2·9; N, 12·6. $C_8H_7O_4N_2Cl$ requires C, 41·6; H, 3·0; N, 12·15%).

7-Chloro-2-hydroxy-3 : 4-dihydroquinoxaline (V; R = Cl, R′ = H).—*N*-(4-Chloro-2-nitrophenyl)glycine (2·3 g.) was shaken in methanol (75 c.c.) with Raney nickel and hydrogen at room temperature and pressure until the theoretical amount of hydrogen had been absorbed. The mixture was filtered, the filtrates were evaporated to dryness, and the residue was crystallised from alcohol, to give the *product* as colourless plates (yield, 74%), m. p. 214—215° (decomp.) (Found: C, 52·4; H, 3·9; N, 15·2; Cl, 19·0. $C_8H_7ON_2Cl$ requires C, 52·6; H, 3·8; N, 15·3; Cl, 19·5%).

7-Chloro-2-hydroxyquinoxaline (VI; R = Cl, R′ = R″ = H).—Silver nitrate (65 g.) in water (250 c.c.) was treated with sufficient ammonia solution to dissolve the initial precipitate, and the solution added with stirring to a suspension of finely ground 7-chloro-2-hydroxy-3 : 4-dihydroquinoxaline (31·6 g.) in water (250 c.c.). The mixture was stirred and boiled under reflux for 1 hour, cooled, and filtered. The black residue was dried and repeatedly extracted with boiling 2-ethoxyethanol. The combined extracts were cooled, and the crystalline product was collected and washed with alcohol. Further

quantities of the same material were obtained by concentration of the 2-ethoxyethanol mother-liquors to small bulk and by similar treatment of the original aqueous filtrate (yield, 22·2 g.). *7-Chloro-2-hydroxyquinoxaline* crystallised from 2-ethoxyethanol as practically colourless rods, m. p. 270° (decomp.) (Found: C, 53·6; H, 3·2; N, 15·1. $C_8H_5ON_2Cl$ requires C, 53·2; H, 2·8; N, 15·5%).

2 : 7-*Dichloroquinoxaline* (VII; R = Cl, R′ = R″ = H).—7-Chloro-2-hydroxyquinoxaline (11·85 g.) and phosphoryl chloride (150 c.c.) were heated under reflux for 20 minutes. Most of the excess of phosphoryl chloride was then removed by evaporation under diminished pressure, and crushed ice added to the residue. The resulting solid was collected, washed until acid-free with water, and dried in a vacuum over sodium hydroxide. Crystallisation from alcohol then gave 2 : 7-*dichloroquinoxaline* as colourless platelets, m. p. 141° (Found: C, 48·8; H, 1·9; N, 14·0; Cl, 35·1. $C_8H_4N_2Cl_2$ requires C, 48·2; H, 2·0; N, 14·1; Cl, 35·6%).

7-Chloro-2-γ-piperidinopropylaminoquinoxaline (Ia; R = H).—2 : 7-Dichloroquinoxaline (4 g.) and γ-piperidinopropylamine (15 c.c.) were heated under reflux for 2 hours, and the mixture was cooled and dissolved in water (50 c.c.) and hydrochloric acid (20 c.c.). The solution was treated with carbon, filtered, and made strongly alkaline with sodium hydroxide. The liberated oil was extracted with ether, and the extract dried (K_2CO_3) and evaporated. Fractionation of the residual oil gave 7-chloro-2-γ-piperidinopropylaminoquinoxaline (yield 5·1 g.), b. p. 220°/0·5 mm. Triturated with light petroleum (b. p. 40—60°) and a little water it solidified and then crystallised from aqueous methanol as colourless rods of the *dihydrate*, m. p. 80—82° (Found: C, 56·0; H, 7·1; N, 16·3; loss on drying in a vacuum at 60°, 10·5. $C_{16}H_{21}N_4Cl,2H_2O$ requires C, 56·4; H, 7·3; N, 16·4; H_2O, 10·6%). Treatment with methanolic picric acid gave the *picrate* which crystallised from 2-ethoxyethanol as yellow prisms, m. p. 216° (Found: C, 49·4; H, 4·6; N, 18·5; Cl, 6·3. $C_{16}H_{21}N_4Cl,C_6H_3O_7N_3$ requires C, 49·5; H, 4·5; N, 18·4; Cl, 6·7%). Treatment of a solution of the distilled base in ethyl acetate with alcoholic hydrogen chloride until no further precipitation occurred gave the *monohydrochloride* which crystallised from alcohol–ethyl acetate as colourless rods, m. p. 204—205° (Found: C, 56·6; H, 6·1; N, 16·4; Cl, 21·0. $C_{16}H_{21}N_4Cl,HCl$ requires C, 56·3; H, 6·45; N, 16·4; Cl, 20·8%) (6736). The *dihydrochloride* was obtained by dissolving the base in a large excess of warm alcoholic hydrogen chloride; precipitation commenced almost immediately; this salt crystallised from alcohol–ethyl acetate as colourless needles, m. p. 233° (Found: C, 50·6; H, 5·8; N, 14·9. $C_{16}H_{21}N_4Cl,2HCl$ requires C, 50·9; H, 6·15; N, 14·8%).

Ethyl 5-Chloro-2-nitroanilinoacetate (IV; R = H, R′ = Cl, R″ = Et).—10N-Sodium hydroxide (108 c.c.) was added with stirring and cooling to a mixture of ethyl aminoacetate hydrochloride (137·5 g.), water (74 c.c.), and benzene (300 c.c.). Anhydrous potassium carbonate was added to form a thick paste with the aqueous layer, and the benzene solution decanted. The residue was washed repeatedly with benzene, and the benzene solutions were combined and dried over potassium carbonate. To the filtered solution (700 c.c.), 4-chloro-1 : 2-dinitrobenzene (100 g.) (Laubenheimer, *Ber.*, 1875, **8**, 1623; 1876, **9**, 760) was added, and the mixture heated under reflux for 4 hours. Most of the solvent was then removed by evaporation, and light petroleum (b. p. 60—80°) added. The *product*, precipitated initially as an oil, rapidly solidified, and was then collected, washed with light petroleum (b. p. 60—80°), and crystallised from alcohol; it formed golden-yellow needles (yield, 61·3 g.), m. p. 100—101° (Found: C, 46·4; H, 4·3; N, 10·9. $C_{10}H_{11}O_4N_2Cl$ requires C, 46·4; H, 4·25; N, 10·8%).

Attempts to condense 4-chloro-1 : 2-dinitrobenzene with glycine and with ethyl aminoacetate hydrochloride failed.

6-Chloro-2-hydroxy-3 : 4-dihydroquinoxaline (V; R = H, R′ = Cl).—The preceding compound (61·3 g.) was stirred vigorously in alcohol (850 c.c.) for 30 hours in presence of Raney nickel with a rapid stream of hydrogen passing through the solution. The mixture was filtered and the filtrate evaporated to small bulk. The crystalline product which separated on cooling was collected, washed with alcohol, and dried. Crystallisation from water gave *6-chloro-2-hydroxy-3 : 4-dihydroquinoxaline* as pale yellow needles (yield, 71%), m. p. 184° (Found: C, 52·4; H, 4·2; N, 15·9. $C_8H_7ON_2Cl$ requires C, 52·6; H, 3·8; N, 15·3%).

6-Chloro-2-hydroxyquinoxaline (VI; R = R″ = H, R′ = Cl).—The preceding dihydro-compound (25·1 g.) was stirred and boiled under reflux with water (500 c.c.), and a solution of ammoniacal silver nitrate [prepared from silver nitrate (52 g.) in water (100 c.c.)] added. After boiling for 2 hours the mixture was cooled and filtered, and the black residue washed with water. After drying, it was extracted with 2-ethoxyethanol (500 c.c.), and the filtrate cooled. The crystalline material which separated on cooling was collected and the filtrates were used for re-extraction. After the process had been repeated three times more, the combined crops of crystals were washed with methanol and dried. The pure *product* thus obtained (yield, 10·5 g.) had m. p. 305°. For analysis it was recrystallised from 2-ethoxyethanol giving minute colourless plates (Found: C, 52·9; H, 3·2; N, 15·4. $C_8H_5ON_2Cl$ requires C, 53·2; H, 2·8; N, 15·5%).

2 : 6-*Dichloroquinoxaline* (VII; R = R″ = H, R′ = Cl).—6-Chloro-2-hydroxyquinoxaline (10 g.) was treated with boiling phosphoryl chloride (100 c.c.) for 20 minutes. The excess of phosphoryl chloride was then removed by distillation under diminished pressure, and crushed ice added to the residue. The resulting solid was collected, washed with water, dried, and crystallised from alcohol to give the *product* as practically colourless needles, m. p. 159—160° (Found: C, 48·4; H, 2·3; N, 13·4; Cl, 35·7. $C_8H_4N_2Cl_2$ requires C, 48·2; H, 2·0; N, 14·1; Cl, 35·6%).

6-Chloro-2-γ-piperidinopropylaminoquinoxaline (IIa; R = H).—2 : 6-Dichloroquinoxaline (3 g.) and γ-piperidinopropylamine (11 c.c.) were boiled under reflux for 2 hours. The cooled reaction mixture was dissolved in a mixture of water (100 c.c.) and acetic acid (15 c.c.), leaving only a little insoluble material. The carbon-treated and filtered solution was made alkaline with sodium hydroxide and extracted with ether. The residue left after evaporation of the dried (K_2CO_3) solution was distilled to remove unchanged γ-piperidinopropylamine. Fractionation of the residue gave *6-chloro-2-γ-piperidinopropylaminoquinoxaline* (yield, 78%), b. p. 192°/0·2 mm., which slowly crystallised and then separated from methanol as practically colourless plates, m. p. 109—110° (Found: C, 59·8; H, 7·1; N, 16·9. $C_{16}H_{21}N_4Cl,H_2O$ requires C, 59·6; H, 7·1; N, 17·4%) (7034). It formed a *dipicrate* which crystallised from 2-ethoxy-

ethanol as small yellow needles, m. p. 191—192° (Found: C, 44·5; H, 3·7; N, 18·8. $C_{16}H_{21}N_4Cl,2C_6H_3O_7N_3$ requires C, 44·05; H, 3·6; N, 18·4%).

Condensation of 2 : 3 : 6-*Trichloroquinoxaline with* γ-*Piperidinopropylamine.*—γ-Piperidinopropylamine (42·7 g.) was gradually added to a solution of 2 : 3 : 6-trichloroquinoxaline (70·2 g.) (see Part XXVII, *loc. cit.*) in boiling alcohol (400 c.c.), and the mixture heated under reflux for 18 hours. The alcohol was then removed by evaporation, the residue dissolved in 5N-acetic acid (200 c.c.), and the filtered solution made alkaline with sodium hydroxide. The precipitated oil gradually solidified when kept and was then collected and crystallised from methanol. The material which separated (yield, 62%) was recrystallised from methanol to give 2 : 6-*dichloro*-3-γ-*piperidinopropylaminoquinoxaline* (I*a*; R = Cl) as colourless needles, m. p. 108° (Found: C, 56·7; H, 6·1; N, 16·2; Cl, 20·8. $C_{16}H_{20}N_4Cl_2$ requires C, 56·6; H, 5·9; N, 16·5; Cl, 20·9%) (6219). The corresponding *picrate* crystallised from 2-ethoxyethanol as yellow prisms, m. p. 228—230° (Found: C, 46·6; H, 4·2; N, 16·8. $C_{16}H_{20}N_4Cl_2,C_6H_3O_7N_3$ requires C, 46·5; H, 4·1; N, 17·3%). The original methanol filtrate from the separation of 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline was concentrated to about one-eighth of its original volume and allowed to stand. The material which separated (yield, 20%) was recrystallised from methanol to give 2 : 7-*dichloro*-3-γ-*piperidinopropylaminoquinoxaline* (II*a*; R = Cl) as colourless rods, m. p. 76—77° (Found: C, 56·7; H, 5·7; N, 16·7. $C_{16}H_{20}N_4Cl_2$ requires C, 56·6; H, 5·9; N, 16·5%) (6991). This afforded a *picrate* which separated from 2-ethoxyethanol as minute yellow prisms, m. p. 191—193° (Found: C, 46·6; H, 4·2; N, 16·8. $C_{16}H_{20}N_4Cl_2,C_6H_3O_7N_3$ requires C, 46·5; H, 4·1; N, 17·3%).

Partial Reductive Dehalogenation of 2 : 6-*Dichloro*-3-γ-*piperidinopropylaminoquinoxaline.*—2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline (6·8 g.) in alcohol (100 c.c.) was shaken with hydrogen and Raney nickel until the calculated amount of hydrogen had been absorbed (7 hours). The catalyst was then removed by filtration, and the solvent evaporated under diminished pressure. The residue was boiled with 2N-hydrochloric acid (100 c.c.) for ½ hour to hydrolyse any unchanged material, and the solution then made alkaline with sodium hydroxide and extracted with ether. Removal of the solvent from the dried (K_2CO_3) ethereal extract left an oil (4·1 g.) which was crystallised from aqueous methanol to give a product, m. p. 80—81°, undepressed in admixture with authentic 7-chloro-2-γ-piperidinopropylaminoquinoxaline (Found: C, 56·8; H, 7·4; N, 16·7. Calc. for $C_{16}H_{21}N_4Cl,2H_2O$: C, 56·4; H, 7·3; N, 16·4%). With alcoholic picric acid it gave a picrate, m. p. 216—217° (from 2-ethoxyethanol), alone or admixed with an authentic specimen (Found: C, 49·2; H, 4·6; N, 18·1. Calc. for $C_{16}H_{21}N_4Cl,C_6H_3O_7N_3$: C, 49·5; H, 4·5; N, 18·4%).

Partial Reductive Dehalogenation of 2 : 7-*Dichloro*-3-γ-*piperidinopropylaminoquinoxaline.*—2 : 7-Dichloro-3-γ-piperidinopropylaminoquinoxaline (6·2 g.) was treated with hydrogen and Raney nickel, and the reaction mixture worked up as in the preceding experiment. The oily crude product (4·2 g.) crystallised from aqueous methanol and then had m. p. 110—111°, alone or in admixture with authentic 6-chloro-2-γ-piperidinopropylaminoquinoxaline (Found: C, 59·6; H, 7·3; N, 17·1. Calc. for $C_{16}H_{21}N_4Cl,H_2O$: C, 59·6; H, 7·1; N, 17·4%). With alcoholic picric acid it gave a picrate, m. p. 191—192° (decomp.) (from 2-ethoxyethanol), undepressed by admixture with the authentic dipicrate (Found: C, 44·1; H, 3·6; N, 18·0. Calc. for $C_{16}H_{21}N_4Cl,2C_6H_3O_7N_3$: C, 44·05; H, 3·6; N, 18·4%).

6-*Chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline* (I*a*; R = SH).—Hydrogen sulphide was passed into a solution of sodium (0·6 g.) in alcohol (40 c.c.) until the theoretical increase in weight (0·85 g.) for formation of sodium hydrogen sulphide had occurred. The solution was then added to a solution of 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline (8·5 g.) in warm alcohol (60 c.c.), and the mixture boiled under reflux for 2 hours with the continual passage of hydrogen sulphide into the mixture. After being filtered hot, the solution was evaporated under reduced pressure to about one-fifth of its volume. The material which separated on cooling was collected and crystallised from alcohol. After drying in a vacuum at 100° it was recrystallised from benzene–light petroleum (b. p. 80—100°) to give 6-*chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline* as yellow needles (yield, 60%), m. p. 139° (Found: C, 56·7; H, 6·2; N, 16·5. $C_{16}H_{21}N_4ClS$ requires C, 57·0; H, 6·3; N, 16·6%) (7175.)

7-*Chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline* (II*a*; R = SH).—Prepared similarly from 2 : 7-dichloro-3-γ-piperidinopropylaminoquinoxaline, this *compound* crystallised from alcohol as clusters of small yellow prisms (yield, 45%), m. p. 178° (Found: C, 57·2; H, 6·0; N, 16·7. $C_{16}H_{21}N_4ClS$ requires C, 57·0; H, 6·3; N, 16·6%).

Desulphurisation of 6-*Chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline.*—The thiol (2 g.), alcohol (120 c.c.), and Raney nickel (*ca.* 20 g.) were boiled under reflux with stirring for 5 hours. By filtration and evaporation of the solvent an oily product was obtained which crystallised from aqueous methanol and had m. p. 79—81°, alone or in admixture with 7-chloro-2-γ-piperidinopropylaminoquinoxaline. It afforded the picrate (crystallised from 2-ethoxyethanol), m. p. and mixed m. p. 216—217° (Found: C, 49·9; H, 4·6%), and dihydrochloride, m. p. 233°, undepressed by admixture with the dihydrochloride of (I*a*; R = H).

A similar attempt to desulphurise 7-chloro-3-γ-piperidinopropylamino-2-mercaptoquinoxaline gave a dark green oil which did not crystallise.

6-*Chloro*-3-γ-*piperidinopropylamino*-2-*ethoxyquinoxaline* (I*a*; R = OEt).—2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline (5·1 g.) was heated under reflux on the steam-bath for 6 hours with a solution of sodium (0·35 g.) in alcohol (30 c.c.). The reaction mixture was then filtered hot and the filtrate diluted with water to precipitate the *product* which was collected and crystallised from methanol to give colourless lozenge-shaped crystals (yield, 90%), m. p. 88° (Found: C, 61·6; H, 6·9; N, 15·8; Cl, 10·2. $C_{18}H_{25}ON_4Cl$ requires C, 62·0; H, 7·2; N, 16·1; Cl, 10·2%) (6946). It formed a *dipicrate*, small yellow plates, m. p. 178° (from 2-ethoxyethanol) (Found: C, 44·6; H, 4·1; N, 17·5. $C_{18}H_{25}ON_4Cl,2C_6H_3O_7N_3$ requires C, 44·6; H, 3·9; N, 17·4%).

The same compound was obtained from an attempted reductive dehalogenation of 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline in presence of sodium hydroxide as follows. 2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline (10·2 g.) was added to a solution of sodium hydroxide (1·2 g.) in alcohol (140 c.c.) containing a little water, and the mixture treated with hydrogen and Raney nickel. Uptake of hydrogen was slow. After 10 hours the mixture was filtered and evaporated to dryness, and

the residue dissolved in ether. The ether solution was shaken with 2N-acetic acid, and the acetic acid extract separated and made alkaline with sodium hydroxide. The precipitated product was isolated by extraction with ether and evaporation of the dried (K_2CO_3) solution. The remaining oil partly crystallised when kept. The crystals were freed from oil by trituration with a little light petroleum (b. p. 40—60°), collected, and recrystallised from methanol. The substance then had m. p. 82°, alone or mixed with authentic 6-chloro-3-γ-piperidinopropylamino-2-ethoxyquinoxaline (Found: C, 61·5; H, 6·9; N, 16·1; Cl, 10·0%). It was not further purified, but converted into its picrate, small yellow plates (from 2-ethoxyethanol), m. p. and mixed m. p. 176—178°.

6-*Chloro*-2 : 3-*diketo*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (VIII).—6-Chloro-2 : 3-dihydroxyquinoxaline (2 g.) was dissolved in hot N-sodium hydroxide (60 c.c.), methyl sulphate (7·55 g.) added, and the mixture heated under reflux with stirring for 4 hours. The precipitated product was collected hot (a further quantity of less pure material separated on cooling), washed, and crystallised from alcohol to give the *quinoxaline* (VIII) as colourless needles, m. p. 192° (Found: C, 53·2; H, 3·8; N, 12·1. $C_{10}H_9O_2N_2Cl$ requires C, 53·5; H, 4·0; N, 12·5%).

6-*Chloro*-2 : 3-*dimethoxyquinoxaline*.—2 : 3 : 6-Trichloroquinoxaline (2·35 g.) was added to a solution of sodium (0·6 g.) in methanol (60 c.c.), and the mixture boiled under reflux for 1½ hours and filtered hot. On cooling the filtrate, the *product* separated as colourless needles (yield, 2·2 g.), m. p. 110—111° (Found: C, 53·8; H, 3·8; N, 12·5. $C_{10}H_9O_2N_2Cl$ requires C, 53·5; H, 4·0; N, 12·5%).

Hydrolysis of 2 : 6-*Dichloro*-3-γ-*piperidinopropylaminoquinoxaline with Hydrochloric acid*.—(*a*) A solution of 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline (4·2 g.) in 2N-hydrochloric acid (100 c.c.) was boiled for one hour and filtered hot. The crystalline product which separated on cooling was collected and then redissolved in water, and the solution carefully neutralised with sodium hydroxide to precipitate the base. A further small quantity was obtained by neutralisation of the reaction mother-liquors. Crystallisation of the combined crops from alcohol gave 6-*chloro*-3-γ-*piperidinopropylamino*-2-*hydroxyquinoxaline* as short colourless needles (yield, 77%), m. p. 193° (Found: C, 60·1; H, 6·4; N, 17·7. $C_{16}H_{21}ON_4Cl$ requires C, 59·9; H, 6·6; N, 17·5%) (7219).

(*b*) 2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline (3·4 g.) in 2N-hydrochloric acid (75 c.c.) was boiled under reflux for 12 hours with stirring. The precipitated solid was collected hot, washed, and dried. It was identified as 6-chloro-2 : 3-dihydroxyquinoxaline (yield, 72%) by methylation with methyl sulphate and alkali (see above) to give 6-chloro-2 : 3-diketo-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, m. p. 189—190°, undepressed by admixture with authentic material.

Ethyl 4-*Chloro*-2-*nitro-oxanilate* (IX).—4-Chloro-2-nitroaniline (17·3 g., 0·1 g.-mol.) and ethyl oxalate (58·4 g., 0·4 g.-mol.) were heated in an oil-bath at 180—190° for 18 hours, the mixture was cooled, and the yellow crystalline product isolated by filtration. Further crops of the same material were obtained by reheating the mother-liquors twice. The crops were combined and extracted with boiling benzene. The insoluble material was collected (2 g.) and crystallised from nitrobenzene to give NN′-*di*-(4-*chloro*-2-*nitrophenyl*)*oxamide* as buff-coloured prisms, m. p. 296° (decomp.) (Found: C, 42·4; H, 2·0; N, 13·6. $C_{14}H_8O_6N_4Cl_2$ requires C, 42·1; H, 2·0; N, 14·0%). The benzene-soluble fraction consisted of the required *ethyl* 4-*chloro*-2-*nitro-oxanilate*. It crystallised from benzene as pale yellow needles (yield, 41%), m. p. 156° (Found: C, 44·4; H, 3·4; N, 10·3. $C_{10}H_9O_5N_2Cl$ requires C, 44·0; H, 3·3; N, 10·3%).

The quantity of *NN′*-di-(4-chloro-2-nitrophenyl)oxamide formed was very considerable when the proportion of ethyl oxalate was reduced below that given above.

N-(4-*Chloro*-2-*nitrophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* (X; R = NO_2).—γ-Piperidinopropylamine (42·7 g., 0·3 g.-mol.) was added gradually to a stirred suspension of ethyl 4-chloro-2-nitro-oxanilate (81·8 g., 0·3 g.-mol.) in benzene (200 c.c.), and stirring then continued for a few minutes. Complete dissolution was obtained. Benzene (120 c.c.) was distilled off, and light petroleum (b. p. 80—100°) (360 c.c.) added to the hot solution. On cooling the mixture, N-(4-*chloro*-2-*nitrophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* separated. Crystallised from benzene–light petroleum (b. p. 60—80°) it formed small pale cream prisms, m. p. 114° (Found: C, 52·6; H, 5·6; N, 15·2. $C_{16}H_{21}O_4N_4Cl$ requires C, 52·1; H, 5·7; N, 15·2%).

When ethyl 4-chloro-2-nitro-oxanilate was treated with an excess of γ-piperidinopropylamine alone, in the cold or at 130° for 3 hours, the products were 4-chloro-2-nitroaniline and NN′-*di*-(γ-*piperidinopropyl*)*oxamide*. The latter, separated by its solubility in 2N-acetic acid, crystallised from light petroleum (b. p. 60—80°) as small colourless needles, m. p. 112—113°, undepressed by admixture with material (m. p. 112—113°) made from γ-piperidinopropylamine and ethyl oxalate (Found: C, 63·7; H, 10·1; N, 16·9. $C_{18}H_{34}O_2N_4$ requires C, 63·9; H, 10·1; N, 16·6%).

Reaction of NN′-*Di*-(4-*chloro*-2-*nitrophenyl*)*oxamide with* γ-*Piperidinopropylamine*.—A mixture of γ-piperidinopropylamine (11·2 g.) and *NN′*-di-(4-chloro-2-nitrophenyl)oxamide (4 g.) was stirred in the cold for 18 hours. The resulting orange solution was diluted with water, the alkalinity to brilliant-yellow just removed by the addition of hydrochloric acid, and the insoluble material (3·1 g.) collected by filtration. It was identified as 4-chloro-2-nitroaniline, m. p. and mixed m. p. 115—116°. The filtrate was concentrated by evaporation under diminished pressure, and sodium hydroxide added to render the solution just alkaline to Clayton-yellow. The resulting precipitate was collected, washed with water, and dried (yield, 3·1 g.). It had m. p. 112°, alone or admixed with *NN′*-di-(γ-piperidinopropyl)-oxamide.

N-(4-*Chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* (X; R = NH_2).—The corresponding nitro-compound (14·7 g.) was reduced in alcohol (120 c.c.) with hydrogen and Raney nickel at room temperature and pressure. Uptake of hydrogen was slow, but was complete after 12 hours. The catalyst was removed by filtration, the filtrate treated with carbon, again filtered, and evaporated to small bulk. The crystalline product which separated on cooling was collected and recrystallised from alcohol to give N-(4-*chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* as small colourless needles, m. p. 99° after short drying at 70° and m. p. 120° after drying *in vacuo* at 80° (Found: C, 56·7; H, 6·8; N, 16·2; Cl, 10·6. $C_{16}H_{23}O_2N_4Cl$ requires C, 56·7; H, 6·8; N, 16·5; Cl, 10·5%).

Cyclisation of N-(4-*Chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide with Aqueous-alcoholic Hydrogen Chloride*.—*N*-(4-Chloro-2-aminophenyl)-*N′*-(γ-piperidinopropyl)oxamide (3·4 g.) was dissolved

in hot alcohol (40 c.c.), water (4 c.c.) and hydrochloric acid (8 c.c.) were added, and the mixture was boiled for 15 minutes. The product, which began to separate after about 3 minutes, was collected, after cooling, washed with alcohol, and dried (yield, 1·7 g.). It was shown to be 6-chloro-2 : 3-dihydroxyquinoxaline, (*a*) by methylation with methyl sulphate and sodium hydroxide to give 6-chloro-2 : 3-diketo-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, m. p. and mixed m. p. 191—192°, and (*b*) by treatment with phosphorus pentachloride to give 2 : 3 : 6-trichloroquinoxaline, m. p. and mixed m. p. 144°.

5(or 6)-*Chloro*-2-*hydroxymethylbenziminazole* (XI; R = CH_2·OH).—A solution of 4-chloro-1 : 2-phenylenediamine (28·5 g.) and glycollic acid (22·8 g.) in 4N-hydrochloric acid (200 c.c.) was heated under reflux for 40 minutes, cooled, and neutralised with aqueous ammonia. The precipitated product was collected, washed with water, and crystallised from aqueous methanol to give 5(or 6)-*chloro*-2-*hydroxymethylbenziminazole* as practically colourless prisms (yield, 30·4 g.), m. p. 206—207° (Found: C, 52·6; H, 3·9; N, 15·6. $C_8H_7ON_2Cl$ requires C, 52·6; H, 3·9; N, 15·35%).

5(or 6)-*Chlorobenziminazole*-2-*carboxylic Acid* (XI; R = CO_2H).—5(or 6)-Chloro-2-hydroxymethylbenziminazole (5·5 g.) was dissolved in boiling water (400 c.c.), and N-sodium hydroxide (7 c.c.) added, followed by a solution of potassium permanganate (7 g.) in water (300 c.c.) which was added slowly with stirring during 1 hour. When the addition was complete, the mixture was boiled for a further ½ hour with stirring and then filtered hot, and the filtrate cooled and acidified with acetic acid. The precipitated product (3·7 g.) was crystallised from water (decolorising carbon), washed with ether, and dried by azeotropic distillation with benzene, to give the 5(or 6)-*chlorobenziminazole* 5(or 6)-*chlorobenziminazole*-2-*carboxylate*, m. p. 158—159° (decomp.) (Found: C, 51·4; H, 2·8; N, 16·2; Cl, 20·6. $C_9H_5O_2N_2Cl,C_7H_5N_2Cl$ requires C, 51·6; H, 3·1; N, 16·1; Cl, 20·3%). A sample of this material was extracted with aqueous sodium hydrogen carbonate, and the insoluble material extracted with ether. The ethereal extract was concentrated and treated with alcoholic picric acid to give 5(or 6)-chlorobenziminazole picrate (see below), m. p. and mixed m. p. 216°. The sodium hydrogen carbonate solution was acidified with acetic acid, and the precipitated product collected, washed with water, and dried in a vacuum over sulphuric acid, to give 5(or 6)-*chlorobenziminazole*-2-*carboxylic acid*, m. p. *ca.* 159° (decomp.) (dependent on the rate of heating) (Found: C, 48·0, 48·9; H, 2·9, 3·4; N, 14·5, 14·8. $C_8H_5O_2N_2Cl$ requires C, 48·9; H, 2·6; N, 14·25%). Consistent analyses could not be obtained.

5′(or 6′) : 5″(or 6″)-*Dichloro*-3 : 6-*diketodibenziminazolo*(1′ : 2′ : 1 : 2)(1″ : 2″ : 4 : 5)*piperazine* (XII).—5(or 6)-Chlorobenziminazole-2-carboxylic acid (5·9 g.) and thionyl chloride (35 c.c.) were boiled under reflux for 8 hours. After the mixture had been cooled, the solid was collected, ground with ice-water, filtered, and dried at 100° (yield, 3·8 g.). Crystallisation from nitrobenzene gave the *product* as pale yellow irregular plates, m. p. >350° (Found: C, 54·0; H, 2·0; N, 15·5. $C_{16}H_6O_2N_4Cl_2$ requires C, 54·0; H, 1·7; N, 15·7%).

5(or 6)-*Chlorobenziminazole*-2-*carboxy*-γ-*piperidinopropylamide* (XI; R = CO·NH·$[CH_2]_3$·N<$[CH_2]_4$>CH_2).—A mixture of the preceding compound (XII) (0·25 g.), γ-piperidinopropylamine (2 c.c.), and water (6 c.c.) was boiled under reflux gently for 20 minutes. Complete dissolution was quickly obtained. The mixture was cooled and diluted with water (35 c.c.), and the precipitated product collected. Crystallised from alcohol, 5(or 6)-*chlorobenziminazole*-2-*carboxy*-γ-*piperidinopropylamide* formed colourless needles, m. p. 173—174° (Found: C, 59·8; H, 6·3; N, 17·6. $C_{16}H_{21}ON_4Cl$ requires C, 59·9; H, 6·6; N, 17·5%).

5(or 6)-*Chlorobenziminazole* (XI; R = H).—A mixture of 4-chloro-1 : 2-phenylenediamine (10 g.) and 85% formic acid (25 c.c.) was boiled under reflux for 2 hours, cooled, and poured into excess of dilute aqueous ammonia. The precipitated product was collected and dried at 80° and then by azeotropic distillation with benzene. Crystallisation from benzene–light petroleum (b. p. 60—80°) then gave 5(or 6)-chlorobenziminazole, m. p. 124—126° (Found: C, 55·1; H, 3·4; N, 18·0. Calc. for $C_7H_5N_2Cl$: C, 55·1; H, 3·3; N, 18·4%). Repeated crystallisation from benzene–light petroleum (b. p. 60—80°) gave material, m. p. 117—118° (Found: C, 55·2; H, 3·1; N, 18·6%), which was considered to be a different form of the same substance (Fischer, *loc. cit.*, gives m. p. 125°). With alcoholic picric acid it gave a *picrate*, yellow needles, m. p. 215—216° (from alcohol) (Found: C, 41·0; H, 2·3; N, 18·8. $C_7H_5N_2Cl,C_6H_3O_7N_3$ requires C, 40·9; H, 2·1; N, 18·4%).

Cyclisation of N-(4-*Chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide by Heat.*—N-(4-Chloro-2-aminophenyl)-N′-(γ-piperidinopropyl)oxamide (5·1 g.) was heated at 190—200° for 10 minutes. On cooling, the melt set to a glass which gradually crystallised. Recrystallisation from alcohol gave 5(or 6)-chlorobenziminazole-2-carboxy-γ-piperidinopropylamide (yield, 63%), m. p. 173—174°, undepressed by admixture with material made by the method described above.

This material (1·35 g.), dissolved in hydrochloric acid (40 c.c.), was boiled under reflux for 24 hours. The solution was diluted with water (100 c.c.), cooled, and made alkaline with aqueous ammonia. After filtration, the filtrate was acidified with acetic acid. The precipitated material was collected and crystallised from water to give colourless needles of 5(or 6)-chlorobenziminazole-2-carboxylic acid (yield, 74%), m. p. 157—158° (decomp.), undepressed by admixture with an authentic specimen. A portion of this acid (0·25 g.) was heated at 155—165° for 15 minutes, the resulting oil extracted with benzene, and the extract filtered and evaporated to small bulk. Addition of light petroleum (b. p. 40—60°) precipitated an oil which solidified on scratching. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave 5(or 6)-chlorobenziminazole, m. p. 117°, undepressed by admixture with authentic material of m. p. 117—118°. It afforded a picrate, m. p. 215—216°, alone or in admixture with authentic 5(or 6)-chlorobenziminazole picrate.

2 : 6-*Dichloro*-3-γ-*diethylaminopropylaminoquinoxaline* (I; R = Cl, R′ = $[CH_2]_3$·NEt_2).—γ-Diethylaminopropylamine (13 g.) was added to a solution of 2 : 3 : 6-trichloroquinoxaline (23·4 g.) in boiling alcohol (600 c.c.) and the whole boiled under reflux for 12 hours. The solvent was then removed by distillation, and the residue extracted with 2N-hydrochloric acid, a little unchanged 2 : 3 : 6-trichloroquinoxaline (2·6 g.) remaining undissolved. The filtered extract was made alkaline with sodium hydroxide, the precipitated oil extracted with ether, and the ethereal extract in turn extracted with

2N-acetic acid. Addition of sodium hydroxide to the acid extract gave the product which was isolated by extraction with ether and evaporation of the dried (K_2CO_3) extract. Vacuum-distillation of the residue gave 2 : 6-*dichloro*-3-*γ*-*diethylaminopropylaminoquinoxaline* as a pale orange oil, b. p. 170—175°/5 × 10^{-3} mm. (yield, 70%), which solidified when kept and then separated from aqueous methanol as practically colourless prisms, m. p. 66—67° (Found: C, 55·0; H, 6·1; N, 16·9; Cl, 21·9. $C_{15}H_{20}N_4Cl_2$ requires C, 55·1; H, 6·2; N, 17·1; Cl, 21·7%) (6231). The corresponding *picrate*, prepared from the base with alcoholic picric acid, crystallised from alcohol as pale yellow rods, m. p. 140—142° (Found: C, 45·1; H, 4·2; N, 17·4. $C_{15}H_{20}N_4Cl_2,C_6H_3O_7N_3$ requires C, 45·3; H, 4·2; N, 17·6%).

2 : 6-*Dichloro*-3-*δ*-*diethylamino*-*α*-*methylbutylaminoquinoxaline* (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2).—A mixture of 2 : 3 : 6-trichloroquinoxaline (11·7 g.), δ-diethylamino-α-methylbutylamine (7·9 g.), and alcohol (120 c.c.) was boiled under reflux for 20 hours with stirring, the solvent removed by distillation, and the residue extracted with 2N-hydrochloric acid. The filtered extract was made alkaline with sodium hydroxide and extracted with ether, and the dried extract evaporated. The resulting oil was twice vacuum-distilled, to give the *product* as a pale yellow oil, b. p. 156—157°/4 × 10^{-4} mm. (Found: C, 57·8; H, 6·8; N, 15·8. $C_{17}H_{24}N_4Cl_2$ requires C, 57·5; H, 6·8; N, 15·8%) (6480). The corresponding *picrate* crystallised from 2-ethoxyethanol as small yellow rods, m. p. 146—147° (Found: C, 47·4; H, 4·7; N, 17·0. $C_{17}H_{24}N_4Cl_2,C_6H_3O_7N_3$ requires C, 47·3; H, 4·7; N, 16·8%).

2 : 6-*Dichloro*-3-*γ*-*di*-n-*butylaminopropylaminoquinoxaline* (I; R = Cl, R′ = $[CH_2]_3$·NBu^n_2).—2 : 3 : 6-Trichloroquinoxaline (4·7 g.) and γ-di-*n*-butylaminopropylamine (3·7 g.) were allowed to react in boiling alcohol (120 c.c.) for 18 hours, the alcohol was distilled off, and the residue crystallised from water containing a little hydrochloric acid to give the *hydrochloride* as colourless irregular plates of indefinite melting point (174—183°) (Found: C, 54·0; H, 6·8; N, 13·4. $C_{19}H_{32}N_4Cl_2$,HCl requires C, 54·4; H, 7·0; N, 13·4%) (6396). The corresponding base decomposed on attempted distillation in a high vacuum.

2 : 6-*Dichloro*-3-*β*-*dimethylaminoethylaminoquinoxaline* (I; R = Cl, R′ = $[CH_2]_2$·NMe_2).—β-Dimethylaminoethylamine (1·8 g.) (Turner, *J. Amer. Chem. Soc.*, 1946, **68**, 1607) was slowly added to a suspension of 2 : 3 : 6-trichloroquinoxaline (4·7 g.) in alcohol (120 c.c.) at 5°, with stirring. The mixture was then stirred at room temperature for 20 hours, the solvent removed by vacuum-evaporation at <30°, and the residue extracted with dilute acetic acid. After being filtered from undissolved material, the extract was made alkaline with sodium hydroxide. The precipitated solid was collected and crystallised first from aqueous methanol and then from light petroleum (b. p. 60—80°), to give 2 : 6-*dichloro*-3-*β*-*dimethylaminoethylaminoquinoxaline* as practically colourless prisms, m. p. 97° (the melt became turbid at 110° and completely solid at 140°, and finally remelted with decomposition at *ca.* 215°) (Found: C, 50·3; H, 4·9; N, 19·4. $C_{12}H_{14}N_4Cl_2$ requires C, 50·55; H, 4·95; N, 19·65%) (6991). With alcoholic picric acid it formed a *picrate* which crystallised from 2-ethoxyethanol as yellow prisms, m. p. 184° (decomp.) (Found: C, 42·1; H, 3·2; N, 19·0. $C_{12}H_{14}N_4Cl_2,C_6H_3O_7N_3$ requires C, 42·05; H, 3·3; N, 19·1%).

Cyclisation of 2 : 6-*Dichloro*-3-*β*-*dimethylaminoethylaminoquinoxaline by Heat.*—2 : 6-Dichloro-3-β-dimethylaminoethylaminoquinoxaline (1·79 g.) was heated to constant weight (1·65 g.) at 135—145°. The residue was extracted four times with light petroleum (b. p. 100—120°) (75, 75, 50, 30 c.c.) until the weight of undissolved material remained unchanged (0·5 g.). The combined light-petroleum extracts deposited crystals on cooling. Recrystallisation from the same solvent gave 6-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra*-*aza*-*anthracene* (XIII; R = Me, R′ = H, *n* = 2) as practically colourless prisms, m. p. 169—170° (Found: C, 56·2; H, 4·6; N, 23·9. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; N, 23·9%). With picric acid in alcoholic solution it afforded a *picrate* which crystallised from 2-ethoxyethanol as yellow needles of indefinite melting point [247—262° (decomp.)] (Found: C, 44·6; H, 3·2; N, 21·2. $C_{11}H_{11}N_4Cl,C_6H_3O_7N_3$ requires C, 44·0; H, 3·0; N, 21·15%). The *acetyl* derivative, prepared by boiling with acetic anhydride for 1 hour and isolated by pouring into water, crystallised from alcohol as almost colourless prisms, m. p. 180—181° (Found: C, 56·6; H, 4·3; N, 20·1. $C_{13}H_{13}ON_4Cl$ requires C, 56·4; H, 4·7; N, 20·25%). The corresponding *benzoyl* derivative, prepared by grinding with benzoyl chloride and aqueous sodium hydroxide, crystallised from alcohol as cream-coloured prisms, m. p. 239—240° (Found: C, 63·4; H, 4·6; N, 16·3. $C_{18}H_{13}ON_4Cl$ requires C, 63·8; H, 4·5; N, 16·5%).

The above material insoluble in light petroleum was readily soluble in water and was purified by crystallisation from ethyl acetate–alcohol. 6-*Chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra*-*aza*-*anthracene dimethochloride* formed practically colourless prisms, m. p. 244° (decomp.) (Found, in material dried at 100°: C, 46·6; H, 5·2; N, 16·5. $C_{11}H_{11}N_4Cl,2CH_3Cl$ requires C, 46·5; H, 5·1; N, 16·7%). With picric acid in alcohol it gave the corresponding *methochloride methopicrate* which crystallised from 2-ethoxyethanol as orange-yellow needles, m. p. 231—232° (decomp.) (Found: C, 43·2; H, 3·7; N, 18·4; Cl, 13·4. $C_{11}H_{11}N_4Cl,CH_3Cl,CH_3·C_6H_2O_7N_3$ requires C, 43·2; H, 3·6; N, 18·6; Cl, 13·4%). The corresponding *methochloride methiodide*, obtained from the dimethochloride by treatment of an aqueous solution with potassium iodide, separated from alcohol as small rectangular prisms, m. p. 239—240° (decomp.) (Found: C, 36·9; H, 4·2; N, 13·2. $C_{11}H_{11}N_4Cl,CH_3Cl,CH_3I$ requires C, 36·6; H, 4·0; N, 13·1%).

Condensation of 2 : 3 : 6-*Trichloroquinoxaline with β-Dimethylaminoethylamine in Boiling Alcoholic Solution.*—2 : 3 : 6-Trichloroquinoxaline (18·6 g.) and β-dimethylaminoethylamine (7·1 g.) were allowed to react in boiling alcohol (250 c.c.) for 20 hours. The solvent was removed by evaporation and the residue extracted with 5N-acetic acid (180 c.c.). The insoluble material consisted of unchanged 2 : 3 : 6-trichloroquinoxaline (6·3 g.). The acetic acid extract was made alkaline with sodium hydroxide and the precipitated product crystallised from methanol. The material which separated first was recrystallised from methanol to give 7-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra*-*aza*-*anthracene* (XIII; R = H, R′ = Me, *n* = 2) as colourless irregular plates or prisms (yield, 0·7 g.), m. p. 222—223° (Found: C, 56·0; 56·1; H, 4·6, 4·8; N, 23·7, 23·8. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; N, 23·9%). With picric acid in alcohol it gave a *picrate* of indefinite melting point (*ca.* 258°) (Found: C, 44·0; H, 2·7; N, 21·2. $C_{11}H_{11}N_4Cl,C_6H_3O_7N_3$ requires C, 44·0; H, 3·0; N, 21·15%). Boiling with acetic anhydride for 1 hour, followed by pouring into water, gave the *acetyl* derivative which crystallised

from alcohol as almost colourless prisms, m. p. 167—169° (Found: C, 56·0; H, 4·5; N, 19·7. $C_{13}H_{13}ON_4Cl$ requires C, 56·4; H, 4·7; N, 20·25%). Mixed with the acetyl derivative of (XIII; R = Me, R′ = H, *n* = 2), it melted at 147—154°. The corresponding *benzoyl* derivative, prepared as in the case of the benzoyl derivative of the isomer, crystallised from alcohol as minute pale cream prisms, m. p. 207—208° (Found: C, 63·6; H, 4·2; N, 16·4. $C_{18}H_{15}ON_4Cl$ requires C, 63·8; H, 4·5; N, 16·5%). Mixed with the benzoyl derivative of (XIII; R = Me, R′ = H, *n* = 2), it melted at 193—226°.

Concentration of the methanol mother-liquors from the separation of (XIII; R = H, R′ = Me, *n* = 2), and addition of an equal volume of water precipitated another substance (yield, 2·35 g.), m. p. 157—158°. Even by repeated crystallisation from methanol the m. p. could not be raised above 160° (Found: C, 56·6; H, 4·7; N, 23·6; Cl, 15·3. Calc. for $C_{11}H_{11}N_4Cl$: C, 56·3; H, 4·7; N, 23·9; Cl, 15·1%), but the material was shown to be substantially 6-chloro-1-methyl-1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene, possibly contaminated with a little of the 7-chloro-isomer. A mixed m. p. of this material with pure material, m. p. 169—170°, showed no depression. In addition, it afforded an acetyl derivative, m. p. 179—181°, and a benzoyl derivative, m. p. 239—240°, alone or mixed with the corresponding derivatives of (XIII; R = Me, R′ = H, *n* = 2).

Condensation of 2 : 3 : 6-*Trichloroquinoxaline with* NN′-*Dimethylethylenediamine*.—2 : 3 : 6-Trichloroquinoxaline (14 g.), *NN′*-dimethylethylenediamine (5·4 g.), and alcohol (200 c.c.) were boiled under reflux with stirring for 18 hours. The diamine dihydrochloride (1·7 g.) which had separated was removed by filtration. When the mixture cooled, unchanged 2 : 3 : 6-trichloroquinoxaline (7·1 g.) separated and was removed. The mother-liquors were evaporated to dryness, and the residue was extracted with 2N-hydrochloric acid. The filtered extract was made alkaline with sodium hydroxide and extracted with ether, and the extract dried (K_2CO_3) and evaporated. Crystallisation of the residual solid from methanol gave 6-*chloro*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (XIII; R = R′ = Me, *n* = 2) as a colourless micro-crystalline powder (yield, 3 g.), m. p. 83° (Found: C, 57·9; H, 5·2; N, 22·6. $C_{13}H_{13}N_4Cl$ requires C, 57·9; H, 5·3; N, 22·5%) (6599). With alcoholic picric acid it gave a *picrate* which separated from 2-ethoxyethanol as yellow rods, m. p. 197—198° (Found: C, 45·5; H, 3·3; N, 20·4. $C_{13}H_{13}N_4Cl,C_6H_3O_7N_3$ requires C, 45·3; H, 3·4; N, 20·5%).

Condensation of 2 : 3 : 6-*Trichloroquinoxaline with Ethylenediamine*.—Ethylenediamine monohydrate (2·7 g.) was added slowly to a solution of 2 : 3 : 6-trichloroquinoxaline (11·7 g.) in boiling alcohol (300 c.c.), and the solution heated under reflux for 14 hours with stirring. Solid began to separate rapidly from the reaction mixture. After the mixture had been cooled, the product was collected, dried, and extracted with boiling light petroleum (b. p. 80—100°) to remove unchanged 2 : 3 : 6-trichloroquinoxaline. The insoluble residue (7·1 g.) crystallised from 2-ethoxyethanol to give NN′-*di*-(2 : 6-*dichloro*-3-*quinoxalyl*)*ethylenediamine* as almost colourless prisms, m. p. 258—260° (Found: C, 47·9; H, 2·9; N, 18·4. $C_{18}H_{12}N_6Cl_4$ requires C, 47·6; H, 2·7; N, 18·5%) (6479).

6-*Chloro*-1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (XIII; R = Et, R′ = H, *n* = 2).—Prepared as described in Part XXVII (*loc. cit.*) by heating 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline at 200°, and crystallised from alcohol, this compound had m. p. 189° (7085). With alcoholic picric acid it gave a *picrate* which crystallised from 2-ethoxyethanol as orange-yellow needles, m. p. 257—258° (Found: C, 45·1; H, 3·4; N, 20·6. $C_{13}H_{13}N_4Cl,C_6H_3O_7N_3$ requires C, 45·3; H, 3·4; N, 20·5%).

6-*Chloro*-1′-*ethyl*-1′ : 5′-*diaza*-2 : 3-*pentamethylenequinoxaline* (XIII; R = Et, R′ = H, *n* = 3).—2 : 6-Dichloro-3-γ-diethylaminopropylaminoquinoxaline (6·5 g.) was heated at 230—240° (oil-bath) for 1½ hours with stirring. After cooling, the dark product was extracted with boiling benzene, and the filtrate evaporated to dryness. The residue was in turn extracted with hot light petroleum (b. p. 60—80°), and the extract filtered. When it cooled, crystals of the *product* separated (yield 1·2 g.). Recrystallised from alcohol this formed pale yellow rhombs, m. p. 148° (Found: C, 59·1; H, 5·5; N, 21·1. $C_{13}H_{15}N_4Cl$ requires C, 59·4; H, 5·8; N, 21·3%) (6730).

6-*Chloro*-2-β-*diethylaminoethylaminoquinoxaline* (II; R = H, R′ = $[CH_2]_2{\cdot}NEt_2$).—2 : 6-Dichloroquinoxaline (3 g.) and β-diethylaminoethylamine (12 g.) were boiled under reflux for 2 hours, and the reaction mixture was cooled and dissolved in 2·5N-acetic acid (100 c.c.). The solution was treated with carbon, filtered, and made alkaline with sodium hydroxide. Extraction with ether and evaporation of the dried (K_2CO_3) solution gave an oil containing unchanged β-diethylaminoethylamine, which was removed by distillation at 10 mm. The higher-boiling residue was then fractionated, to give 6-*chloro*-2-β-*diethylaminoethylaminoquinoxaline* as a very pale yellow oil (yield, 79%), b. p. 157—160°/0·2 mm., which rapidly solidified and then separated from light petroleum (b. p. 60—80°) as practically colourless plates, m. p. 78—79° (Found: C, 60·3; H, 7·0; N, 20·6. $C_{14}H_{19}N_4Cl$ requires C, 60·3; H, 6·8; N, 20·1%) (7109).

7-*Chloro*-2-β-*diethylaminoethylaminoquinoxaline* (I; R = H, R′ = $[CH_2]_2{\cdot}NEt_2$).—Similarly prepared from 2 : 7-dichloroquinoxaline and β-diethylaminoethylamine, it formed a pale yellow oil (yield, 68%), b. p. 180°/0·6 mm. The *dihydrochloride*, prepared by treating a solution of the base in ethyl acetate with alcoholic hydrogen chloride to render it just acid to Congo-red, crystallised from alcohol–ethyl acetate as almost colourless rods, m. p. 180—182° (Found: C, 48·3; H, 6·5; N, 16·0. $C_{14}H_{19}N_4Cl,2HCl$ requires C, 47·8; H, 6·0; N, 15·9%) (6860).

7-*Chloro*-2-γ-*diethylaminopropylaminoquinoxaline* (I; R = H, R′ = $[CH_2]_3{\cdot}NEt_2$), prepared in an analogous manner from 2 : 7-dichloroquinoxaline and γ-diethylaminopropylamine, was obtained as a pale yellow oil (yield, 79%), b. p. 190°/0·3 mm. The *dihydrochloride* separated from alcohol–ethyl acetate as pale yellow needles, m. p. 197—198° (Found: C, 46·8; H, 6·6; N, 14·3. $C_{15}H_{21}N_4Cl,2HCl$ requires C, 47·0; H, 6·5; N, 14·6%) (6990).

2-β-*Diethylaminoethylaminoquinoxaline* (III; R = H, R′ = $[CH_2]_2{\cdot}NEt_2$), prepared similarly from 2-chloroquinoxaline (Gowenlock, Newbold, and Spring, *J.*, 1945, 622) and β-diethylaminoethylamine, formed a pale yellow oil (yield, 79%), b. p. 135°/0·1 mm. (Found: C, 66·7; H, 8·2; N, 22·4. $C_{14}H_{20}N_4,0{\cdot}5H_2O$ requires C, 66·4; H, 8·3; N, 22·1%) (7216). The *dipicrate*, prepared from the base in

methanol, crystallised from 2-ethoxyethanol as yellow plates, m. p. 183—186° (Found: C, 44·6; H, 3·5; N, 20·2. $C_{14}H_{20}N_4,2C_6H_3O_7N_3$ requires C, 44·4; H, 3·7; N, 20·0%).

2-γ-Diethylaminopropylaminoquinoxaline (III; R = H, R′ = $[CH_2]_3$·NEt_2), prepared analogously, was obtained as a pale yellow oil (yield, 70%) b. p. 153°/0·1 mm. (Found: C, 67·7; H, 8·5; N, 21·1. $C_{15}H_{22}N_4,0·5H_2O$ requires C, 67·5; H, 8·6; N, 21·0%) (7215). In methanol it afforded a *dipicrate* which separated from alcohol as yellow needles, m. p. 127—129° (Found: C, 44·7; H, 3·2; N, 19·8. $C_{15}H_{22}N_4,2C_6H_3O_7N_3$ requires C, 45·25; H, 3·9; N, 19·6%).

2-β-Diethylaminoethylamino-3-methylquinoxaline (III; R = Me, R′ = $[CH_2]_2$·NEt_2).—Similarly prepared from 2-chloro-3-methylquinoxaline (Newbold and Spring, *J.*, 1948, 521) and β-diethylaminoethylamine, the *base* formed a pale yellow hygroscopic oil (yield, 81%), b. p. 148—150°/0·4 mm. (Found: C, 67·3; H, 8·2; N, 20·7. $C_{15}H_{22}N_4,0·5H_2O$ requires C, 67·4; H, 8·6; N, 21·0%) (7214). Its *dipicrate* crystallised from alcohol as small yellow rods, m. p. *ca.* 130° (Found: C, 45·5; H, 4·4; N, 19·2. $C_{15}H_{22}N_4,2C_6H_3O_7N_3$ requires C, 45·25; H, 3·9; N, 19·6%).

2-γ-Diethylaminopropylamino-3-methylquinoxaline (III; R = Me, R′ = $[CH_2]_3$·NEt_2).—Prepared in a corresponding manner by use of γ-diethylaminopropylamine in place of β-diethylaminoethylamine, the *base* formed a pale yellow hygroscopic oil (yield, 66%), b. p. 155°/0·05 mm. (Found: C, 68·5; H, 8·4; N, 19·8. $C_{16}H_{24}N_4,0·5H_2O$ requires C, 68·3; H, 8·9; N, 19·9%) (7221). The *dipicrate* crystallised from methanol as yellow needles, m. p. 155° (Found: C, 46·1; H, 4·1; N, 19·5. $C_{16}H_{24}N_4,2C_6H_3O_7N_3$ requires C, 46·0; H, 4·1; N, 19·2%).

2-β-Diethylaminoethylamino-3-hydroxyquinoxaline (III; R = OH, R′ = $[CH_2]_2$·NEt_2).—2-Chloro-3-β-diethylaminoethylaminoquinoxaline (3·1 g.) in 2N-hydrochloric acid (80 c.c.) was boiled gently under reflux for 1 hour. The solution was cooled and made just alkaline to litmus with sodium hydroxide. The *product*, which separated initially as an oil, soon solidified. It was collected and crystallised from aqueous alcohol as colourless micro-crystalline powder, m. p. 76—77° (Found: C, 60·6; H, 7·8; N, 20·0. $C_{14}H_{20}ON_4,H_2O$ requires C, 60·4; H, 8·0; N, 20·1%) (7310).

Condensation of 2 : 3-Dichloroquinoxaline with γ-Piperidinopropylamine.—γ-Piperidinopropylamine (3·6 g.) was added slowly to a solution of 2 : 3-dichloroquinoxaline (5 g.) in boiling alcohol (100 c.c.), and the mixture heated under reflux for 5½ hours. The solvent was then removed by distillation, and the solid residue extracted with hot dilute hydrochloric acid. The insoluble material (unchanged 2 : 3-dichloroquinoxaline, 0·8 g.) was removed by filtration and the filtrate neutralised with sodium hydroxide. The precipitated solid was collected, washed, and dried. Crystallisation from methanol afforded first *2-γ-piperidinopropylamino-3-hydroxyquinoxaline* (III; R = OH, R′ = $[CH_2]_3$·N < $[CH_2]_4$ > CH_2) as elongated tablets (yield, 39%), m. p. 179—180° (Found: C, 67·0; H, 7·6; N, 19·5. $C_{16}H_{22}ON_4$ requires C, 67·1; H, 7·7; N, 19·6%) (7173). Concentration of the mother-liquors from this compound gave *2-chloro-3-γ-piperidinopropylaminoquinoxaline* (III; R = Cl, R′ = $[CH_2]_3$·N < $[CH_2]_4$ > CH_2) which separated from light petroleum (b. p. 40—60°) as colourless needles (yield, 7%), m. p. 88° (Found: C, 63·1; H, 7·0; N, 18·2. $C_{16}H_{21}N_4Cl$ requires C, 63·0; H, 6·9; N, 18·4%). The *picrate* crystallised from 2-ethoxyethanol as minute yellow rods, m. p. 201—202° (Found: C, 49·4; H, 4·5; N, 18·2. $C_{16}H_{21}N_4Cl,C_6H_3O_7N_3$ requires C, 49·5; H, 4·5; N, 18·4%).

Acid Hydrolysis of 2 : 3 : 6-Trichloroquinoxaline.—2 : 3 : 6-Trichloroquinoxaline (4·7 g.) and 5N-hydrochloric acid (50 c.c.) were boiled under reflux for 4 hours with stirring. After the mixture had cooled, the solid was collected, dried, and extracted with hot light petroleum (b. p. 80—100°) (80 c.c.). Evaporation of the light petroleum gave unchanged 2 : 3 : 6-trichloroquinoxaline (2·1 g.). The material insoluble in light petroleum (1·95 g.) was shown to be 6-chloro-2 : 3-dihydroxyquinoxaline by methylation with methyl sulphate and sodium hydroxide to give 6-chloro-2 : 3-diketo-1 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, m. p. and mixed m. p. 189—190°, in good yield.

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275. *Synthetic Antimalarials. Part XL. The Effect of Variation of Substituents in 2-Chloro-3-β-diethylaminoethylaminoquinoxaline.*

By (the late) F. H. S. CURD, D. G. DAVEY, and G. J. STACEY.

The novel lead provided by the observation that 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline (Haworth and Robinson, *J.*, 1948, 777) possessed marked antimalarial activity has been followed up by the preparation of a number of analogous compounds containing different substituents in the 6-position. The synthetic method utilised in the original work and extended in the previous paper has been successfully applied in the case of the substances now described. The various compounds have been tested for antimalarial activity against *P. gallinaceum* in chicks, and it has been found that none of the 6-substituents investigated promoted antimalarial activity as high as that of the original 6-chloro-compound. Of the individual compounds, highest activity was shown by 2 : x-*dichloro*-3-β-*diethylaminoethylamino*-6(or 7)-*methoxyquinoxaline* which was derived from 2 : 3 : x-*trichloro*-6-*methoxyquinoxaline*, the product of interaction of 2 : 3-dihydroxy-6-methoxyquinoxaline with phosphorus pentachloride. Nuclear chlorination was avoided by the use of phosphoryl chloride which gave 2 : 3-*dichloro*-6-*methoxyquinoxaline*.

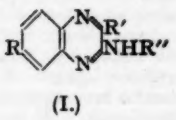
ALTHOUGH the antimalarial activity of 4-dialkylaminoalkylaminoquinolines is well known, and has been made the subject of much study by German and American workers, correspondingly

substituted 2-dialkylaminoalkylaminoquinolines are apparently without such activity (see, *e.g.*, Lutz, Ashburn, and Rowlett, *J. Amer. Chem. Soc.*, 1946, **68**, 1322; Wiselogle, "Survey of Antimalarial Drugs," 1941—45, pp. 1135, 1144, 1187, and confirmed by our own unpublished work). It was therefore of more than usual interest that 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline (I; R = R′ = Cl, R″ = $[CH_2]_2$·NEt_2) (Haworth and Robinson, Part XXVII, *J.*, 1948, 777) should possess marked antimalarial activity (*P. gallinaceum* in chicks) in view of its α-dialkylaminoalkylamino-heterocyclic structure, and a thorough investigation of this novel type appeared to provide an excellent opportunity for the further study of the relationship between chemical constitution and antimalarial activity.

In the preceding paper it has been shown that both chlorine atoms have a profound influence on the antimalarial activity of this type of compound : removal of the 2-chlorine atom or its replacement by other groups in 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline led to a complete loss of activity while 2-chloro-3-β-diethylaminoethylaminoquinoxaline (I; R = H, R′ = Cl, R″ = $[CH_2]_2$·NEt_2) exhibited only a fraction of the activity of its 6-chloro-derivative.

In the present paper, the investigation has been extended, and the effect on antimalarial activity of substituents other than chlorine in the benz-nucleus of 2-chloro-3-dialkylaminoalkylaminoquinoxalines has been studied. On account of the importance of the methoxyl group in other types of antimalarials, this substituent was the obvious first choice for investigation. Without purification, 4-methoxy-1 : 2-phenylenediamine, prepared by reduction of 2-nitro-4-methoxyaniline, was treated with ethyl oxalate to give 2 : 3-dihydroxy-6-methoxyquinoxaline (II; R = OMe) which was characterised as its methylation product, 2 : 3-*diketo*-6-*methoxy*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (III; R = OMe). There seemed little doubt as to the constitution of this compound in view of its non-identity with 2 : 3 : 6-*trimethoxyquinoxaline* (V; R = OMe), which was prepared by the action of methanolic sodium methoxide on 2 : 3-*dichloro*-6-*methoxyquinoxaline* (IV; R = OMe). This was satisfactorily prepared by the action of phosphoryl chloride on (II; R = OMe), whereas phosphorus pentachloride, which is usually necessary for such conversions, led to nuclear chlorination. Condensation of 2 : 3-dichloro-6-methoxyquinoxaline with β-diethylaminoethylamine, γ-diethylaminopropylamine and γ-piperidinopropylamine gave respectively 2-*chloro*-3-β-*diethylaminoethylamino*-, 2-*chloro*-3-γ-*diethylaminopropylamino*-, and 2-*chloro*-3-γ-*piperidinopropylamino*-6-*methoxyquinoxalines* (I; R = OMe, R′ = Cl, R″ = $[CH_2]_2$·NEt_2, $[CH_2]_3$·NEt_2, $[CH_2]_3$·N<$[CH_2]_4$>CH_2, respectively), and mild acid hydrolysis of the first afforded 3-β-*diethylaminoethylamino*-2-*hydroxy*-6-*methoxyquinoxaline* (I; R = OMe, R′ = OH, R″ = $[CH_2]_2$·NEt_2).

The constitution of (I; R = OMe, R′ = Cl, R″ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2) was proved (and those of the related compounds followed by analogy) by a method similar to that employed in Part XXXIX (preceding paper) to demonstrate that the 3-chlorine atom is more reactive than the 2-chlorine atom in the interaction of 2 : 3 : 6-trichloroquinoxaline with aminoalkylamines. Subjected to reductive dehalogenation, using hydrogen and Raney nickel in alcoholic solution in presence of one equivalent of sodium hydroxide, it gave a product which was demonstrated to be 2-γ-*piperidinopropylamino*-7-*methoxyquinoxaline* (I; R = OMe, R′ = H, R″ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2), and not 3-γ-*piperidinopropylamino*-6-*methoxy*-2-*ethoxyquinoxaline* (I; R = OMe, R′ = OEt, R″ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2) (cf. preceding paper), by synthesis of the former by a method which left no doubt as to its constitution. Interaction of 4-nitro-2-methoxyaniline with bromoacetic acid gave 2-*nitro*-4-*methoxyphenylglycine* (VI) which on treatment with hydrogen in presence of Raney nickel was reduced and cyclised in one operation to give 2-*hydroxy*-7-*methoxy*-3 : 4-*dihydroquinoxaline* (VII); oxidation of this with ammoniacal silver nitrate afforded 2-*hydroxy*-7-*methoxyquinoxaline* (VIII; R = OH) from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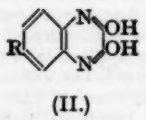
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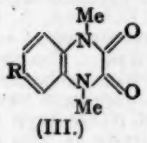
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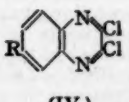
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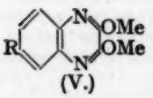
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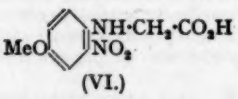
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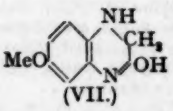
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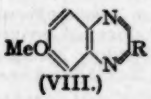
(VIII.)

which 2-*chloro*-7-*methoxyquinoxaline* (VIII; R = Cl) was obtained, by the action of phosphoryl chloride, and condensed with γ-piperidinopropylamine to give (I; R = OMe, R′ = H,

R″ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2). The above-mentioned 3-γ-piperidinopropylamino-6-methoxy-2-ethoxyquinoxaline was prepared by the action of alcoholic sodium ethoxide on 2-chloro-3-γ-piperidinopropylamino-6-methoxyquinoxaline.

Having demonstrated in two cases that condensation between a 6-substituted-2 : 3-dichloroquinoxaline and an aminoalkylamine occurred preferentially in the 3-position, it was concluded that 2 : 3-*dichloro-6-bromoquinoxaline* (IV; R = Br) and 2 : 3-*dichloro-6-methylquinoxaline* (IV; R = Me) behaved similarly and that their respective condensation products with β-diethylaminoethylamine were 2-*chloro-6-bromo-3-β-diethylaminoethylaminoquinoxaline* (I; R = Br, R′ = Cl, R″ = $[CH_2]_2$·NEt_2) and 2-*chloro-3-β-diethylaminoethylamino-6-methylquinoxaline* (I; R = Me, R′ = Cl, R″ = $[CH_2]_2$·NEt_2).

Finally, 4-nitro-1 : 2-phenylenediamine was condensed with ethyl oxalate to give 6-nitro-2 : 3-dihydroxyquinoxaline (II; R = NO_2) which, without being characterised, was treated with phosphorus pentachloride to yield 2 : 3-*dichloro-6-nitroquinoxaline* (IV; R = NO_2). On treatment of this with β-diethylaminoethylamine in boiling alcoholic solution it yielded a mono-condensation product, 2-*chloro*-6(or 7)-*nitro*-3-β-*diethylaminoethylaminoquinoxaline*. The constitution of this compound has not been definitely proved, and since the nitro-group may have a different effect on the relative reactivities of the chlorine atoms in 2 : 3-dichloro-6-nitroquinoxaline from that of the other substituents studied, we do not feel justified in assuming that the 3-chlorine atom has reacted preferentially.

Comparison of the antimalarial activities given in the Table with those given in the preceding paper for 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline shows that the 6-chlorine atom is the most potent for antimalarial activity. The corresponding 6-bromo-compound (7284) is somewhat less active and the methoxy-analogue (6731) has a significantly low activity. The inferiority of 2-chloro-3-β-diethylaminoethylamino-6-methoxyquinoxaline, which is reflected in the more rapid fall-off of activity with increase in size of the dialkylaminoalkylamino-group than that which occurs in the 2 : 6-dichloro-3-dialkylaminoalkylaminoquinoxaline series, is similar to that which obtains in 7-substituted 4-dialkylaminoalkylaminoquinolines (Wiselogle, *op. cit.*, pp. 1145, 1187) and -quinazolines (Chapman, Gibson, and Mann, *J.*, 1947, 890). The inactivation of 2-chloro-3-β-diethylaminoethylamino-6-methoxyquinoxaline (6731) which occurs on replacing the 2-chlorine atom by a hydroxyl group (7397) is similar to that noted in the previous paper in the case of analogous compounds.

Antimalarial Activities.

The activity of the various compounds was estimated against the blood forms of *P. gallinaceum* in chicks by the method described by one of us (D.G.D.) (*Ann. Trop. Med. Parasit.*, 1946, **40**, 52). The results given below are expressed in the same way as in previous papers of this series.

Ref. no.	Quinoxaline.	Dose, mg./kg.	Activity.
6731	2-Chloro-3-β-diethylaminoethylamino-6-methoxy-	160	++
		80	++
		40	−
6830	2-Chloro-3-γ-diethylaminopropylamino-6-methoxy-	160	−
7415	2-Chloro-3-γ-piperidinopropylamino-6-methoxy-	80	−
7284	2-Chloro-6-bromo-3-β-diethylaminoethylamino-	40	++
		20	+
		10	−
7172	2-Chloro-3-β-diethylaminoethylamino-6-methyl-	160	++
		80	±
7176	2-Chloro-6(or 7)-nitro-3-β-diethylaminoethylamino-	160	+
		80	−
7220	2 : *x*-Dichloro-3-β-diethylaminoethylamino-6(or 7)-methoxy-	40	++
		20	++
7397	3-β-Diethylaminoethylamino-2-hydroxy-6-methoxy-	160	−
7535	2-γ-Piperidinopropylamino-7-methoxy-	80	−
7621	3-γ-Piperidinopropylamino-6-methoxy-2-ethoxy-	40	−

In addition, some of the compounds were tested for prophylactic activity against *P. gallinaceum* in chicks by the method previously described (Davey, *ibid.*, p. 453), Nos. 6731 and 6830 at 160 mg./kg., No. 7220 at 40 mg./kg., and No. 7397 at 80 mg./kg., but none was active.

Experimental.

2 : 3-*Dihydroxy-6-methoxyquinoxaline* (II; R = OMe).—2-Nitro-4-methoxyaniline (84·1 g.) (Reverdin, *Ber.*, 1896, **29**, 2595) was added gradually with stirring to a solution of stannous chloride (450 g.) in hydrochloric acid (900 c.c.), the temperature being kept at or below 20°. When the addition was

complete, the mixture was stirred for 2 hours and then slowly added to 30% aqueous sodium hydroxide (2 l.), the temperature being kept below 40°. The alkaline mixture was extracted with benzene, and the benzene extract washed once with water and evaporated. Ethyl oxalate (500 c.c.) was added to the residual crude 4-methoxy-1 : 2-phenylenediamine, and the mixture heated under reflux in an oil-bath at 175—185° for 3½ hours. The finely divided solid which had separated was filtered off, after cooling, washed with light petroleum, and dried. The only satisfactory method of purification discovered was by dissolution in aqueous sodium hydroxide and reprecipitation with hydrochloric acid (yield, 76%). For characterisation, the 2 : 3-dihydroxy-6-methoxyquinoxaline (2·9 g.) was dissolved in N-sodium hydroxide (70 c.c.) and methylated with methyl sulphate (7·6 g.) to give 2 : 3-*diketo*-6-*methoxy*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (III; R = OMe), which crystallised from alcohol as colourless needles, m. p. 182—183° (Found: C, 59·9; H, 5·2; N, 12·7. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%).

2 : 3-*Dichloro*-6-*methoxyquinoxaline* (IV; R = OMe).—2 : 3-Dihydroxy-6-methoxyquinoxaline (72 g.) and phosphoryl chloride (150 c.c.) were heated together at 120—125° for 1 hour, and the excess of the latter then removed by distillation under reduced pressure. The residue was treated with ice-cold water, and the solid product collected and washed well with water. After drying, it was extracted with boiling benzene, and the extract carbon-treated and filtered. Concentration of the benzene filtrate gave pale cream flakes of 2 : 3-*dichloro*-6-*methoxyquinoxaline* (yield, 81%), m. p. 160° (Found: C, 47·3; H, 2·7; N, 11·7. $C_9H_6ON_2Cl_2$ requires C, 47·2; H, 2·6; N, 12·2%).

2 : 3 : x-*Trichloro*-6-*methoxyquinoxaline*.—An intimate mixture of 2 : 3-dihydroxy-6-methoxyquinoxaline (57·6 g.) and phosphorus pentachloride (135 g.) was heated at 170—180° for 1 hour, obvious reaction occurring when the temperature reached 160°. The reaction mixture was then distilled under diminished pressure to remove phosphoryl chloride, and the residue triturated, and finally ground, with water. The product was then collected, washed with water, and dried. Two extractions with boiling benzene (600 c.c., 400 c.c.) and evaporation of the combined extracts to dryness gave the *trichloro*-compound (29 g.), which was recrystallised from benzene; pale cream plates, m. p. 188° (Found: C, 41·0; H, 2·2; N, 10·3; Cl, 40·3. $C_9H_5ON_2Cl_3$ requires C, 41·0; H, 1·9; N, 10·6; Cl, 40·4%).

2 : 3 : 6-*Trimethoxyquinoxaline* (V; R = OMe).—2 : 3-Dichloro-6-methoxyquinoxaline (2·3 g.) was added to a solution of sodium (0·6 g.) in methanol (70 c.c.), and the whole heated under reflux for 1½ hours. The reaction mixture was then filtered and set aside to crystallise. The *quinoxaline* recrystallised from methanol in colourless needles, m. p. 125—126° (Found: C, 60·2; H, 5·6; N, 12·4. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%).

2 : x-*Dichloro*-3-β-*diethylaminoethylamino*-6(*or* 7)-*methoxyquinoxaline*.—β-Diethylaminoethylamine (3·5 g.) was gradually added to a suspension of 2 : 3 : x-trichloro-6-methoxyquinoxaline (7·9 g.) in boiling alcohol (120 c.c.), and the mixture boiled under reflux for 16 hours. The solvent was then distilled off, the residue extracted with dilute acetic acid, and the filtered extract made alkaline with sodium hydroxide. The precipitated oil solidified on standing and was collected, washed, and dried. Crystallisation from light petroleum (b. p. 40—60°) gave the *dichloro*-compound as pale yellow prisms, m. p. 70° (Found: C, 52·7; H, 5·7; N, 16·3. $C_{15}H_{20}ON_4Cl_2$ requires C, 52·4; H, 5·9; N, 16·3%) (7220). With alcoholic picric acid it gave a *picrate*, which separated from 2-ethoxyethanol as minute yellow rods, m. p. 150° (Found: C, 44·3; H, 4·2; N, 16·7. $C_{15}H_{20}ON_4Cl_2,C_6H_3O_7N_3$ requires C, 44·1; H, 4·05; N, 17·1%).

2-*Chloro*-3-β-*diethylaminoethylamino*-6-*methoxyquinoxaline* (I; R = OMe, R′ = Cl, R″ = $[CH_2]_2{\cdot}NEt_2$).—To a boiling mixture of alcohol (120 c.c.) and 2 : 3-dichloro-6-methoxyquinoxaline (9·2 g.), β-diethylaminoethylamine (4·7 g.) was gradually added. Complete solution was obtained after a few minutes' refluxing, which was continued altogether for 20 hours. The alcohol was then removed by evaporation, and the residue extracted with hot dilute hydrochloric acid. The filtered extract was cooled and made alkaline with sodium hydroxide. The precipitated product was collected, dried, and crystallised from light petroleum (b. p. 60—80°), giving 2-*chloro*-3-β-*diethylaminoethylamino*-6-*methoxyquinoxaline* (6731) as fine colourless needles (yield, 5·9 g.), m. p. 73—74° (Found: C, 58·5; H, 6·5; N, 18·4. $C_{15}H_{21}ON_4Cl$ requires C, 58·3; H, 6·85; N, 18·1%). The corresponding *picrate* crystallised from 2-ethoxyethanol as tufts of pale yellow needles, m. p. 158° (Found: C, 47·2; H, 4·5; N, 18·1. $C_{15}H_{21}ON_4Cl,C_6H_3O_7N_3$ requires C, 46·9; H, 4·5; N, 18·2%).

2-*Chloro*-3-γ-*diethylaminopropylamino*-6-*methoxyquinoxaline* (I; R = OMe, R′ = Cl, R″ = $[CH_2]_3{\cdot}NEt_2$) (6830), prepared in a similar manner but with γ-diethylaminopropylamine in place of β-diethylaminoethylamine, crystallised from light petroleum (b. p. 40—60°) as pale cream prisms (yield, 67%), m. p. 66° (Found: C, 59·6; H, 6·9; N, 17·3. $C_{16}H_{23}ON_4Cl$ requires C, 59·5; H, 7·2; N, 17·4%). It formed a *picrate* which crystallised from 2-ethoxyethanol as yellow needles, m. p. 170° (Found: C, 47·9; H, 5·0; N, 17·5. $C_{16}H_{23}ON_4Cl,C_6H_3O_7N_3$ requires C, 47·9; H, 4·7; N, 17·8%).

2-*Chloro*-3-γ-*piperidinopropylamino*-6-*methoxyquinoxaline* (I; R = OMe, R′ = Cl, R″ = $[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$).—2 : 3-Dichloro-6-methoxyquinoxaline (11·5 g.) and γ-piperidinopropylamine (7·2 g.) were caused to react together in boiling alcohol (120 c.c.), and the crude product isolated in the above-described manner. Crystallisation from light petroleum (b. p. 60—80°) gave 2-*chloro*-3-γ-*piperidinopropylamino*-6-*methoxyquinoxaline* (7415) as practically colourless prisms (yield, 59%), m. p. 118—119° (Found: C, 61·0; H, 6·8; N, 16·6. $C_{17}H_{23}ON_4Cl$ requires C, 61·0; H, 6·9; N, 16·7%), which afforded a *picrate*, minute lemon-yellow plates from 2-ethoxyethanol, m. p. 206—208° (decomp.) (Found: C, 48·9; H, 4·4; N, 17·9. $C_{17}H_{23}ON_4Cl,C_6H_3O_7N_3$ requires C, 49·0; H, 4·6; N, 17·4%). On concentration of the light petroleum mother-liquors from the above main product a mixture of prisms and silky needles was obtained. Separated by hand and recrystallised from light petroleum (b. p. 60—80°), the latter gave, in very small quantity, an isomer of (I; R = OMe, R′ = Cl, R″ = $[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$) which was presumed to be 2-*chloro*-3-γ-*piperidinopropylamino*-7-*methoxyquinoxaline*; recrystallised from light petroleum (b. p. 60—80°), it formed colourless needles, m. p. 130—131° (Found: C, 60·6; H, 6·7; N, 16·9. $C_{17}H_{23}ON_4Cl$ requires C, 61·0; H, 6·9; N, 16·7%). Mixed with 2-chloro-3-γ-piperidinopropylamino-6-methoxyquinoxaline it melted at 105—112°.

3-β-*Diethylaminoethylamino*-2-*hydroxy*-6-*methoxyquinoxaline* (I; R = OMe, R′ = OH, R″ = $[CH_2]_2{\cdot}NEt_2$).—2-Chloro-3-β-diethylaminoethylamino-6-methoxyquinoxaline (4·6 g.) and 2N-hydrochloric

acid (120 c.c.) were heated under reflux together for 1½ hours. After cooling, the reaction mixture was filtered, and the filtrate neutralised with sodium hydroxide. The precipitated *base* was collected and purified by crystallisation from aqueous methanol; colourless needles, m. p. 112° (Found: C, 62·4; H, 7·3; N, 19·0. $C_{15}H_{22}O_2N_4$ requires C, 62·05; H, 7·6; N, 19·3%) (7397).

N-(2-Nitro-4-methoxyphenyl)glycine (VI).—Bromoacetic acid (34·8 g.) was added gradually during 2 hours with stirring to melted 2-nitro-4-methoxyaniline (84 g.) at 120—125°. Towards the end of the addition the mixture became very thick, and xylene (50 c.c.) was added to render it more fluid. After being heated at 125—130° for a further ½ hour, the reaction mixture was made alkaline to brilliant-yellow with aqueous ammonia and steam-distilled to remove the xylene. After dilution to 500 c.c. with water, the residue was filtered at 60°. The insoluble residue and the solid which separated on cooling were combined and re-extracted with dilute aqueous ammonia at 60°, the insoluble residue being given a third extraction with aqueous ammonia. The combined extracts were acidified with hydrochloric acid, the precipitated product collected, washed with water, and dried (yield, 32·7 g.). Recrystallisation from alcohol gave *N-(2-nitro-4-methoxyphenyl)glycine* as clusters of orange-red needles, m. p. 172° (decomp.) (Found: C, 48·1; H, 4·9; N, 12·6. $C_9H_{10}O_5N_2$ requires C, 47·8; H, 4·45; N, 12·4%). The corresponding *ethyl* ester, formed from the acid by heating it in alcohol solution in presence of a little hydrochloric acid, crystallised from light petroleum (b. p. 60—80°) as bright reddish-orange needles, m. p. 75° (Found: C, 52·3; H, 6·0; N, 11·2. $C_{11}H_{14}O_5N_2$ requires C, 52·0; H, 5·55; N, 11·0%).

2-Hydroxy-7-methoxy-3 : 4-dihydroquinoxaline (VII).—*N*-(2-Nitro-4-methoxyphenyl)glycine (4·5 g.) in alcohol (100 c.c.) and Raney nickel were shaken with hydrogen at 60° and a pressure of 60 atm. After cooling, the reaction mixture was filtered, and the filtrate evaporated to dryness under diminished pressure. Crystallisation of the residue from water (decolorising carbon) gave the *hydroxy*-compound as practically colourless plates, m. p. 169—171° (Found: C, 60·0; H, 5·4; N, 16·3. $C_9H_{10}O_2N_2$ requires C, 60·7; H, 5·65; N, 15·7%). It was difficult to avoid some oxidation to the corresponding quinoxaline derivative during crystallisation.

2-Hydroxy-7-methoxyquinoxaline (VIII; R = OH).—To the preceding compound (1·6 g.), suspended in boiling water (30 c.c.), was added a solution of ammoniacal silver nitrate [prepared by adding ammonia to a solution of silver nitrate (3·4 g.) in water (12 c.c.) so as just to dissolve the initial precipitate]. The mixture was boiled under reflux with stirring for ½ hour, cooled, and filtered. Repeated extraction of the dried residue with boiling 2-ethoxyethanol, followed by concentration of the combined extracts, yielded *2-hydroxy-7-methoxyquinoxaline* (0·9 g.). Recrystallised from 2-ethoxyethanol, it formed practically colourless plates, m. p. 235—236° (Found: C, 61·0; H, 4·7; N, 15·9. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%).

2-Chloro-7-methoxyquinoxaline (VIII; R = Cl).—2-Hydroxy-7-methoxyquinoxaline (3·5 g.) and phosphoryl chloride (30 c.c.) were boiled together gently under reflux for ½ hour. Excess phosphoryl chloride was then distilled off under diminished pressure, and the residue treated with ice and water. The product so obtained was collected, washed acid free with water, and dried. Recrystallised from light petroleum (b. p. 80—100°), *2-chloro-7-methoxyquinoxaline* formed colourless rods (3·1 g.), m. p. 102° (Found: C, 55·5; H, 3·5; N, 14·0. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%).

2-γ-Piperidinopropylamino-7-methoxyquinoxaline (I; R = OMe, R′ = H, R″ = $[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$).—2-Chloro-7-methoxyquinoxaline (1·2 g.) and γ-piperidinopropylamine (6 c.c.) were heated gently under reflux together for 2 hours. After cooling, the reaction mixture was dissolved in 5N-acetic acid, and the solution made alkaline with sodium hydroxide to precipitate an oil, which solidified on standing. The product was collected, washed with water, and purified by crystallisation from aqueous methanol (carbon), giving *2-γ-piperidinopropylamino-7-methoxyquinoxaline* (7535) as a colourless microcrystalline powder (yield, 89%), m. p. 80—81° (Found: C, 60·7; H, 8·2; N, 16·6. $C_{17}H_{24}ON_4,2H_2O$ requires C, 60·7; H, 8·4; N, 16·7%). With alcoholic picric acid it gave a *dipicrate*, which crystallised from 2-ethoxyethanol as minute yellow prisms, m. p. 219—220° (decomp.) (Found: C, 45·9; H, 4·1; N, 18·5. $C_{17}H_{24}ON_4,2C_6H_3O_7N_3$ requires C, 45·9; H, 4·0; N, 18·5%).

Reductive Dehalogenation of 2-Chloro-3-γ-piperidinopropylamino-6-methoxyquinoxaline.—A mixture of 2-chloro-3-γ-piperidinopropylamino-6-methoxyquinoxaline (3·4 g.), finely ground sodium hydroxide (0·4 g.), and alcohol (100 c.c.) was treated with hydrogen and Raney nickel at N.T.P. When hydrogen uptake had ceased (after 4 hours) the reaction mixture was filtered and evaporated to dryness under reduced pressure. The semi-solid residue crystallised from aqueous methanol to give a product, m. p. 80—81° undepressed in admixture with authentic 2-γ-piperidinopropylamino-7-methoxyquinoxaline prepared as described above (Found: C, 60·8; H, 8·3; N, 16·3%). It formed a dipicrate which, after crystallisation from 2-ethoxyethanol, had m. p. 219—221° either alone or in admixture with the dipicrate of 2-γ-piperidinopropylamino-7-methoxyquinoxaline (Found: C, 45·9; H, 4·0; N, 18·9%). Omission of the sodium hydroxide made dehalogenation inconveniently slow.

3-γ-Piperidinopropylamino-6-methoxy-2-ethoxyquinoxaline (I; R = OMe, R′ = OEt, R″ = $[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$).—2-Chloro-3-γ-piperidinopropylamino-6-methoxyquinoxaline (5 g.) was added to a solution of sodium (0·35 g.) in alcohol (30 c.c.), the mixture heated under reflux for 5 hours, and then filtered. Dilution with water precipitated the *base* which, after drying, crystallised from light petroleum (b. p. 60—80°) as small colourless rods (yield, 85%), m. p. 93—94° (Found: C, 66·0; H, 7·8; N, 15·8. $C_{19}H_{28}O_2N_4$ requires C, 66·25; H, 8·2; N, 16·3%) (7621). The *dipicrate* separated from 2-ethoxyethanol as small lemon-yellow plates, m. p. 164—168° (Found: C, 46·9; H, 4·7; N, 17·3. $C_{19}H_{28}O_2N_4,2C_6H_3O_7N_3$ requires C, 46·4; H, 4·3; N, 17·45%).

6-Bromo-2 : 3-dihydroxyquinoxaline (II; R = Br).—4-Bromo-2-nitroaniline was prepared by the following sequence of reactions: acetanilide ⟶ *p*-bromoacetanilide ⟶ 4-bromo-2-nitroacetanilide ⟶ 4-bromo-2-nitroaniline. The procedures used in the first and the second stage were respectively those of Remmeres (*Ber.*, 1874, **7**, 346) and Hubner (*Annalen*, 1881, **209**, 356). For the hydrolysis in the third stage, we preferred to employ acid hydrolysis using equal parts of water and concentrated hydrochloric acid rather than alkaline hydrolysis as described by Hubner (*loc. cit.*).

4-Bromo-2-nitroaniline (108·5 g.) was reduced with stannous chloride (450 g.) and hydrochloric acid (900 c.c.), and the reaction mixture worked up as described above to give crude 4-bromo-1 : 2-phenylene-

diamine (cf. Hubner, *loc. cit.*). Without purification this was heated with ethyl oxalate (400 c.c.) at 175—185° for 3½ hours and then cooled. The solid which had separated was collected, washed with light petroleum, and dried, giving 6-bromo-2 : 3-dihydroxyquinoxaline as a brownish powder (yield, 80%). For characterisation, a solution of a sample (2·4 g.) in warm N-sodium hydroxide (60 c.c.) was methylated at the boil with methyl sulphate (7·55 g.) for 4½ hours to give *6-bromo-2 : 3-diketo-1 : 4-dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (III; R = Br), which crystallised from alcohol as colourless needles, m. p. 205—206° (Found : C, 44·6; H, 3·4; N, 10·1. $C_{10}H_9O_2N_2Br$ requires C, 44·6; H, 3·4; N, 10·4%).

2 : 3-*Dichloro-6-bromoquinoxaline* (IV; R = Br).—6-Bromo-2 : 3-dihydroxyquinoxaline (60 g.) and phosphorus pentachloride (45·9 g.) were intimately mixed and heated together at 165—175° under reflux for ½ hour. Phosphoryl chloride was then removed by distillation under diminished pressure, the residue ground with ice-water, and the product collected, dried, and extracted with benzene. Concentration of the dried, carbon-treated extract gave the *dichloro*-compound, which crystallised from light petroleum (b. p. 80—100°) as practically colourless irregular plates (yield, 56%), m. p. 132° (Found : C, 34·6; H, 1·2; N, 10·0. $C_8H_3N_2Cl_2Br$ requires C, 34·5; H, 1·1; N, 10·1%).

6-Bromo-2 : 3-*dimethoxyquinoxaline* (V; R = Br).—Prepared by interaction of 2 : 3-dichloro-6-bromoquinoxaline with sodium methoxide as described above in the case of the 2 : 3 : 6-trimethoxyquinoxaline, this *bromo*-compound separated from methanol as colourless needles, m. p. 114—115° (Found : C, 44·9; H, 3·5; N, 10·0. $C_{10}H_9O_2N_2Br$ requires C, 44·6; H, 3·4; N, 10·4%).

2-Chloro-6-bromo-3-β-diethylaminoethylaminoquinoxaline (I; R = Br, R′ = Cl, R″ = $[CH_2]_2{\cdot}NEt_2$).—Prepared as described above for similar cases, but from 2 : 3-dichloro-6-bromoquinoxaline and β-diethylaminoethylamine, this *compound* crystallised from light petroleum (b. p. 40—60°) as pale cream prisms, m. p. 87° (Found : C, 46·8; H, 4·7; N, 15·3. $C_{14}H_{18}N_4ClBr$ requires C, 47·0; H, 5·1; N, 15·7%) (7284). The corresponding *picrate* crystallised from 2-ethoxyethanol as small yellow needles, m. p. 153—154° (Found : C, 40·5; H, 3·9; N, 16·5. $C_{14}H_{18}N_4ClBr,C_6H_3O_7N_3$ requires C, 40·95; H, 3·6; N, 16·7%).

2 : 3-*Dihydroxy-6-methylquinoxaline* (II; R = Me).—3-Nitro-4-toluidine (76 g.) (Gattermann, *Ber.*, 1885, **18**, 1483) was reduced at 50° with stannous chloride (450 g.) and hydrochloric acid (900 c.c.), and the product isolated as in similar reductions described above. The resulting crude 4-methyl-1 : 2-phenylenediamine (cf. Beilstein and Kuhlberg, *Annalen*, 1871, **158**, 351) was heated for 3 hours at 170—180° with ethyl oxalate (400 c.c.), and the reaction mixture cooled and filtered. The crude 2 : 3-dihydroxy-6-methylquinoxaline (yield, 94%) thus obtained as a pale yellow powder was converted into *2 : 3-diketo-1 : 4 : 6-trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (III; R = Me), by methylation with methyl sulphate and sodium hydroxide, for the purposes of characterisation. This crystallised from alcohol as colourless needles, m. p. 196—197° (Found : C, 64·6; H, 5·6; N, 13·8. $C_{11}H_{12}O_2N_2$ requires C, 64·6; H, 5·9; N, 13·7%).

2 : 3-*Dichloro-6-methylquinoxaline* (IV; R = Me).—2 : 3-Dihydroxy-6-methylquinoxaline (88 g.) and phosphoryl chloride (200 c.c.) were heated together at 120—130° under reflux for 1 hour. Excess of phosphoryl chloride was removed by distillation under diminished pressure, and the residue triturated with ice-cold water. The resulting product was dried, extracted with boiling benzene (350 c.c.), and the benzene extract carbon-treated and evaporated to dryness. Crystallisation of the residue from light petroleum (b. p. 80—100°) gave 2 : 3-*dichloro-6-methylquinoxaline* as colourless feathery plates (yield, 51%), m. p. 114° (Found : C, 50·5; H, 2·6; N, 13·3. $C_9H_6N_2Cl_2$ requires C, 50·75; H, 2·8; N, 13·1%). The use of phosphorus pentachloride led to some nuclear chlorination and the isolation of a mixed product.

2 : 3-*Dimethoxy-6-methylquinoxaline* (V; R = Me).—Prepared from 2 : 3-dichloro-6-methylquinoxaline and methanolic sodium methoxide, the *dimethoxy*-compound crystallised from aqueous methanol as colourless needles, m. p. 82—83° (Found : C, 64·8; H, 6·1; N, 13·3. $C_{11}H_{12}O_2N_2$ requires C, 64·6; H, 5·9; N, 13·7%).

2-Chloro-3-β-diethylaminoethylamino-6-methylquinoxaline (I; R = Me, R′ = Cl, R″ = $[CH_2]_2{\cdot}NEt_2$).—2 : 3-Dichloro-6-methylquinoxaline (16 g.) was dissolved in boiling alcohol (120 c.c.), and β-diethylaminoethylamine (8·7 g.) gradually added. The mixture was then heated under reflux for 18 hours, the solvent distilled off, and the residue extracted with cold 5N-acetic acid (50 c.c.). The filtered extract was made alkaline with sodium hydroxide, and the precipitated oil extracted with ether. Evaporation of the dried (K_2CO_3) ether extract and vacuum distillation of the residual oil gave the *base* as a pale yellow oil, b. p. 158—160°/5 × 10^{-3} mm. (yield, 43%) (Found : C, 61·5; H, 7·1; N, 19·2. $C_{15}H_{21}N_4Cl$ requires C, 61·5; H, 7·2; N, 19·1%) (7172). With alcoholic picric acid it gave a *picrate*, which crystallised from 2-ethoxyethanol as minute yellow rods, m. p. 150—151° (Found : C, 48·2; H, 4·6; N, 18·5. $C_{15}H_{21}N_4Cl$, $C_6H_3O_7N_3$ requires C, 48·3; H, 4·6; N, 18·8%).

3-β-Diethylaminoethylamino-2-hydroxy-6-methylquinoxaline (I; R = Me, R′ = OH, R″ = $[CH_2]_2{\cdot}NEt_2$) was obtained in a similar experiment in which the product was extracted with hot N-hydrochloric acid instead of cold 5N-acetic acid. It crystallised from light petroleum (b. p. 60—80°) as short colourless needles, m. p. 103—104° (Found : C, 65·1; H, 7·9; N, 20·2. $C_{15}H_{22}ON_4$ requires C, 65·7; H, 8·1; N, 20·4%). The *dipicrate* crystallised from 2-ethoxyethanol as small yellow prisms containing solvent of crystallisation, m. p. 106—107° (Found : C, 45·3; H, 4·8; N, 16·6. $C_{15}H_{22}ON_4,2C_6H_3O_7N_3,C_4H_{10}O_3$ requires C, 45·2; H, 4·65; N, 17·0%).

2 : 3-*Dichloro-6-nitroquinoxaline* (IV; R = NO_2).—4-Nitro-1 : 2-phenylenediamine (107 g.) (Brand, *J. pr. Chem.*, 1906, **74**, 470) and ethyl oxalate (600 c.c.) were heated together at 175—185° under reflux for 4 hours with stirring. After cooling, the solid product was collected and purified by dissolution in hot aqueous sodium hydroxide followed by reprecipitation with hydrochloric acid. 6-Nitro-2 : 3-dihydroxyquinoxaline (yield 66%) was thus obtained as buff-coloured crystals, m. p. 344—346° (decomp.) (not analysed). It could not be methylated satisfactorily to give a 1 : 4-dimethyl derivative.

6-Nitro-2 : 3-dihydroxyquinoxaline (83 g.) and phosphorus pentachloride (185 g.) were heated together under reflux at 170—180° for 1 hour, and the reaction mixture then distilled under reduced pressure to remove phosphoryl chloride. The residue was ground with ice-water, collected, and extracted with benzene. Evaporation of the benzene extract gave 2 : 3-*dichloro-6-nitroquinoxaline*, which crystallised from light petroleum (b. p. 80—100°) as small, pale cream, irregular plates

(yield, 75%), m. p. 152° (Found: C, 39·1; H, 1·5; N, 17·1. $C_8H_3O_2N_3Cl_4$ requires C, 39·3; H, 1·2; N, 17·2%).

2-Chloro-6(or 7)-nitro-3-β-diethylaminoethylaminoquinoxaline, prepared from 2 : 3-dichloro-6-nitroquinoxaline and β-diethylaminoethylamine as in the case of similar compounds, crystallised from methanol as tufts of yellow needles (yield, 42%), m. p. 102° (Found: C, 52·0; H, 5·5; N, 21·2. $C_{14}H_{18}O_2N_5Cl$ requires C, 51·9; H, 5·6; N, 21·6%) (7176). The corresponding *picrate* crystallised from 2-ethoxyethanol as clusters of yellow needles, m. p. 154° (Found: C, 43·6; H, 3·8; N, 20·2. $C_{14}H_{18}O_2N_5Cl,C_6H_3O_7N_3$ requires C, 43·5; H, 3·8; N, 20·3%).

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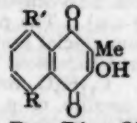
276. *Naturally Occurring Quinones: A Synthesis of Droserone.*

By R. H. THOMSON.

Droserone has been synthesised and its structure established as 3 : 5-dihydroxy-2-methyl-1 : 4-naphthaquinone.

Two colouring matters occur in the outer layers of the bulb of *Drosera Whittakeri*, a plant growing in the Adelaide district of Australia. These pigments were first examined by Rennie (*J.*, 1887, **51**, 371; 1893, **63**, 1083), who showed that the yellow substance, droserone, was probably a dihydroxymethylnaphthaquinone, whilst the more abundant red material (hydroxydroserone) contained an additional hydroxyl group. Many years later Macbeth *et al.* confirmed Rennie's findings, and deduced the positions of the hydroxyl and methyl groups by comparing the natural products with a large number of hydroxynaphthaquinones, making particular use of absorption spectra and reduction potentials. It was thus shown that hydroxydroserone had the structure 3 : 5 : 8-trihydroxy-2-methyl-1 : 4-naphthaquinone (I), whilst droserone, which formed a monoboroacetate and a monopyridine salt, was considered to be either 3 : 5- or 3 : 8-dihydroxy-2-methyl-1 : 4-naphthaquinone (II or III) (Macbeth, Price, and Winzor, *J.*, 1935, 325; Macbeth and Winzor, *J.*, 1935, 334; Lugg, Macbeth, and Winzor, *J.*, 1936, 1457). Hydroxydroserone was synthesised by condensation of 3 : 6-dihydroxy-2-methoxytoluene with maleic anhydride (Winzor, *J.*, 1935, 336) and the structure (I) thereby established, but it was not found possible to distinguish between (II) and (III).



(I; R = R' = OH.)
(II; R = OH, R' = H.)
(III; R = H, R' = OH.)

The hydroxyjuglones originally prepared by Mylius (*Ber.*, 1885, **18**, 463) have recently been characterised as 2 : 5- and 3 : 5-dihydroxy-1 : 4-naphthaquinones (Thomson, *J. Org. Chem.*, 1948, **13**, 870). By treatment of these compounds with acetyl peroxide (Fieser and Oxford, *J. Amer. Chem. Soc.*, 1942, **64**, 2060), a methyl group has now been introduced into the vacant position in the quinonoid ring: 3 : 8-*dihydroxy-2-methyl*-1 : 4-*naphthaquinone* (III), m. p. 193°, was prepared from 2 : 5-dihydroxy-1 : 4-naphthaquinone and afforded a *diacetate*, m. p. 164°; similarly, the 3 : 5-dihydroxy-compound (II), m. p. 181° (diacetate, m. p. 119°), was prepared from the unmethylated quinone. The properties of (II) agreed with those recorded for droserone (Macbeth, *et al.*, *loc. cit.*), and their diacetates were identical (mixed m. p.) and gave concordant absorption characteristics, although only a minute amount of the "natural" material was available for examination. The absorption curves, determined by use of a Beckman Model DU spectrophotometer, showed the following maxima (solvent, 95% ethanol):

	$\lambda_{max.}$, mμ.	241	265	346
3 : 5-Diacetoxy-2-methyl-1 : 4-naphthaquinone	log E	4·150	4·118	3·552
Droserone diacetate		4·155	4·125	3·566

It is noteworthy that the theoretical value for the reduction potential of droserone (with which the value determined experimentally was in good agreement) was calculated from the reduction potential of "hydroxyjuglone" on the assumption that the hydroxyl groups occupied the same relative positions in both compounds (Lugg, Macbeth, and Winzor, *loc. cit.*). This assumption is now seen to be correct, for the hydroxyjuglone obtained by Macbeth *et al.* has proved to be 3 : 5-dihydroxy-1 : 4-naphthaquinone (Thomson, *loc. cit.*).

3 : 5-Dihydroxy-1 : 4-naphthaquinone is best prepared from 3-chlorojuglone. Peroxide alkylation of the latter with acetyl peroxide, followed by treatment of the 3-*chloro*-5-*hydroxy*-2-*methyl*-1 : 4-*naphthaquinone* obtained with sodium hydroxide, provides an alternative route to

droserone, but the overall yield is lower. It also appeared to be of interest to convert juglone into droserone *via* plumbagin (5-hydroxy-2-methyl-1 : 4-naphthaquinone). Plumbagin has been synthesised by two methods, each involving a large number of stages (Fieser and Dunn, *J. Amer. Chem. Soc.*, 1936, **58**, 572; Dieterle, *Scientia Pharm.*, 1938, **9**, 121), so a one-stage synthesis from juglone by peroxide alkylation seemed attractive. Results, however, were disappointing. The product, obtained in very poor yield, was a mixture of mono- and di-methyljuglones which were exceedingly difficult to separate. Careful sublimation yielded a minute amount of material, m. p. 76—77°, which appeared to be plumbagin. Similar unsatisfactory results have been obtained by monoalkylation of other quinones having more than one free position in the quinonoid ring (private communication from Professor L. F. Fieser).

Experimental.

3 : 5-*Dihydroxy*-2-*methyl*-1 : 4-*naphthaquinone* (II).—(*a*) Acetyl peroxide (0·75 g.) was added to a suspension of 3 : 5-dihydroxy-1 : 4-naphthaquinone (1 g.) in glacial acetic acid (10 c.c.). The mixture was warmed over a free flame until effervescence commenced and then transferred to the steam-bath. The effervescence subsided after a few minutes. Heating was continued for 1 hour, and the orange-red solution then allowed to cool. The crude product which separated (0·39 g., m. p. 172—174°) was recrystallised from light petroleum (b. p. 100—120°), 50% aqueous acetic acid, and finally from glacial acetic acid, 3 : 5-dihydroxy-2-methyl-1 : 4-naphthaquinone forming yellow needles, m. p. 181° (yield, 26%) (Found : C, 64·8; H, 4·05. Calc. for $C_{11}H_8O_4$: C, 64·7; H, 3·9%). The diacetate was obtained by boiling (II) with twice its weight of acetic anhydride, containing a trace of concentrated sulphuric acid, for 2 minutes. It crystallised from light petroleum (b. p. 50—60°) in pale yellow needles, m. p. 119°; mixed m. p. with droserone diacetate, 119° (Found : C, 62·2; H, 4·1. Calc. for $C_{15}H_{12}O_6$: C, 62·5; H, 4·15%).

(*b*) To a hot solution of 3-chloro-5-hydroxy-2-methyl-1 : 4-naphthaquinone (see below) (0·5 g.) in alcohol (40 c.c.), an aqueous solution of sodium hydroxide (20 c.c., 10%) was added. The initial violet colour changed to red in about 1 minute. After being warmed on the water-bath for 1 hour, the solution was diluted with cold water (80 c.c.), acidified with hydrochloric acid, and set aside for 3 hours. The brownish-yellow precipitate was collected, dried in a vacuum, and extracted with light petroleum (b. p. 100—120°). The residue, after removal of the solvent, was recrystallised from 50% aqueous acetic acid, and then from glacial acetic acid, forming yellow needles, m. p. 181° (yield, 24%).

3 : 8-*Dihydroxy*-2-*methyl*-1 : 4-*naphthaquinone* (III).—This was prepared as described above for (II) but from 2 : 5-dihydroxy-1 : 4-naphthaquinone (0·92 g.) and acetyl peroxide (0·69 g.) in glacial acetic acid (9 c.c.). The product which crystallised on cooling (0·45 g., m. p. 179—181°) was recrystallised first from glacial acetic acid, and then several times from alcohol, from which 3 : 8-*dihydroxy*-2-*methyl*-1 : 4-*naphthaquinone* separated in minute light orange plates, m. p. 193° (yield, 23%) (Found : C, 64·8; H, 3·7. $C_{11}H_8O_4$ requires C, 64·7; H, 3·9%). The *diacetate* crystallised from methyl alcohol in pale yellow needles, m. p. 164° (Found : C, 62·2; H, 4·1. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·15%).

3-*Chlorojuglone*.—Chlorine (3·6 g.) was passed into a cold suspension of juglone (8·7 g.) in glacial acetic acid (100 c.c.). The suspension was then shaken for 20 minutes; the juglone passed into solution and the yellow dichloride began to separate. After being kept for 2 hours, the mixture was poured into cold water (800 c.c.). The yellow precipitate of juglone dichloride was collected, drained rapidly, and suspended in alcohol (100 c.c.), and the suspension heated under reflux for 20 mins. 3-Chlorojuglone was collected on cooling, and recrystallised from alcohol in orange needles, m. p. 166° (yield, 66%).

3-*Chloro*-5-*hydroxy*-2-*methyl*-1 : 4-*naphthaquinone*.—3-Chlorojuglone (1 g.) in glacial acetic acid (10 c.c.) was treated with acetyl peroxide (0·63 g.) in the usual manner. After being heated on the steam-bath for ¾ hour, the solution was concentrated to half bulk, and the crystals which deposited on cooling were recrystallised first from glacial acetic acid and then twice from aqueous acetic acid. The *quinone* separated in glistening orange-yellow leaflets, m. p. 125° (yield, 35%) (Found : C, 59·4; H, 3·2. $C_{11}H_7O_3Cl$ requires C, 59·3; H, 3·15%). The *acetate* crystallised from alcohol in light-yellow microcrystals, m. p. 144° (Found : C, 58·7; H, 3·4. $C_{13}H_9O_4Cl$ requires C, 59·0; H, 3·4%).

Peroxide Alkylation of Juglone.—A solution of juglone (5 g.) in glacial acetic acid (45 c.c.) was treated with acetyl peroxide (3·72 g.) in the usual way. After 1 hr.'s heating the solution was diluted with water and steam-distilled. The distillate (4000 c.c.) was acidified and extracted with ether, the extract washed, dried ($CaCl_2$), and the solvent removed. The orange-red residue was sublimed at 75—80°, and the sublimate resublimed at 60°, the process taking several days. The second sublimate when crystallised twice from aqueous-methanol formed orange-yellow needles (*ca.* 2 mg.), m. p. 76—77° (plumbagin has m. p. 78—79°). Peroxide alkylation of juglone acetate gave a similar mixture of methyljuglones. Steam-distillation of the reaction mixture, which required several days, gave a very dilute aqueous solution of the mixed acetates, which were hydrolysed on standing.

Juglone acetate also hydrolyses with ease : when 0·2 g. was dissolved in a few c.c. of alcohol or dioxan and the solution poured into water (1 l.), the pale yellow solution obtained became orange-yellow on standing overnight, and ether extraction (without previous acidification) after 48 hours gave a mixture of juglone and a smaller amount of juglone acetate.

The author is greatly indebted to Professor A. Killen Macbeth, of Adelaide University, for a sample of droserone diacetate, and to Dr. F. Wokes and Mr. C. Daglish, of the Ovaltine Research Laboratories, for the absorption-spectra measurements. Thanks are also due to Dr. J. W. Minnis, of the Biochemistry Dept., Edinburgh University, for the microanalyses, and to Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals.

Marischal College, Aberdeen. [*Received, December 6th*, 1948.]

277. *Toxic Fluorine Compounds containing the C–F Link. Part V.* (a) *Fluorine-containing Ammonium Salts* (with I. G. E. Wilding). (b) *Relationship between Physiological Action and Chemical Constitution.*

By B. C. Saunders.

(*a*) An account is given of some hitherto-undescribed compounds containing both the fluoroethyl group and nitrogen. These compounds fall into two distinct groups: (i) toxic materials such as *ethyl fluoroacetamidoacetate* (I) and *2-fluoroethyl aminoacetate hydrochloride* (II); (ii) relatively non-toxic quaternary salts such as *trimethyl-2-fluoroethylammonium bromide* (IV).

(*b*) The toxic properties of the compounds containing the C–F link described in Parts I—V are reviewed, and certain well-defined conclusions are drawn regarding the relationship between physiological action and chemical constitution.

It is well known that the amino- and the acetamido-group and quaternary ammonium salt groups often render compounds physiologically active. Particular reference may be made to the work of Haworth and his collaborators on the toxic action associated with quaternary ammonium salts (*J.*, 1946, 176, 182).

In view of these facts and of the known toxic action of "fluoroacetates" it seemed worth while investigating compounds containing both fluorine and the above-mentioned groups. We prepared the first such compound in 1943 (Report No. 6 on Fluoroacetates to the Ministry of Supply, Sept. 30, 1943), namely, *ethyl fluoroacetamidoacetate*, $CH_2F{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2Et$ (I). It was a colourless crystalline solid which when injected into mice had an L.D. 50 of 20 mg./kg. The corresponding figure for methyl fluoroacetate is 6 mg./kg. The symptoms were similar in each case (delayed convulsant action).

2-Fluoroethyl aminoacetate hydrochloride (II) was readily prepared by esterifying glycine with fluoroethanol (FEA) according to the Fischer–Speier method:

$$NH_2{\cdot}CH_2{\cdot}CO_2H + CH_2F{\cdot}CH_2{\cdot}OH \xrightarrow{HCl} [NH_2{\cdot}CH_2{\cdot}CO_2CH_2{\cdot}CH_2F]^+\,Cl^- \quad \text{(II.)}$$

Using similar conditions with betaine and FEA none of the expected ester was obtained, the betaine remaining unchanged. The reaction between anhydrous trimethylamine and fluoroethyl chloroacetate, however, gave *2-fluoroethylbetaine hydrochloride* in excellent yield:

$$NMe_3 + CH_2Cl{\cdot}CO_2CH_2{\cdot}CH_2F \longrightarrow [NMe_3{\cdot}CH_2{\cdot}CO_2CH_2{\cdot}CH_2F]^+\,Cl^- \quad \text{(III.)}$$

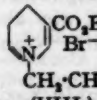
The hydrochloride (II) had an L.D. 50 of approx. 10 mg./kg. by subcutaneous injection into mice. The corresponding figure for 2-fluoroethylbetaine hydrochloride was 45 mg./kg. Both (II) and (III) produced fluoroacetate-like symptoms.

In preparing other compounds containing fluorine and quaternary ammonium groups, advantage was taken of the fact that of the two halogens in 1-bromo-2-fluoroethane, the bromine atom is the more reactive. When, *e.g.*, trimethylamine and bromofluoroethane were allowed to react at room temperature, addition took place and *trimethyl-2-fluoroethylammonium bromide* (IV) was produced. Triethylamine gave *2-fluorotetraethyl ammonium bromide* on being heated with bromofluoroethane.

$\bar{B}r\{\dot{N}Me_3{\cdot}CH_2{\cdot}CH_2F$ (IV.) $C_5H_5\dot{N}{\cdot}CH_2{\cdot}CH_2F\}\bar{B}r$ (V.) $[\dot{N}HMe_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}\dot{N}HMe_2]\bar{B}r_2$ (VI.)

Pyridine gave *2-fluoroethylpyridinium bromide* (V) on being heated under reflux with bromofluoroethane.

Dimethylaniline did not give the expected phenyldimethyl-2-fluoroethylammonium bromide, but gave the compound (VI) in small yield, the point of attack being the para-hydrogens of the dimethylaniline. This seems surprising in view of the unreactivity of the fluorine in bromofluoroethane. A possible explanation is that $[CH_2F{\cdot}CH_2{\cdot}C_6H_4{\cdot}NMe_2]^+Br^-$ (VII) is first formed and that in this compound the fluorine atom is much more reactive than in the original bromofluoroethane. The fluorine atom of (VII) would then react with the *p*-hydrogen atom of a second molecule of dimethylaniline.



(VIII.)

These fluoro-quaternary bromides proved to be not very toxic and had L.D. 50's of the order of 300 mg./kg.

In view of the biological importance of nicotinic acid, it was decided to prepare a quaternary salt from the acid or ester and bromofluoroethane. *3-Carbethoxy-N-2-fluoroethylpyridinium bromide* (VIII) was therefore prepared and examined. The L.D. 50 for subcutaneous injection into mice was 200 mg./kg., *i.e.*, it was relatively non-toxic compared with methyl fluoroacetate.

It seems possible to draw certain deductions from the above toxicities. It is to be noted that ethyl fluoroacetamidoacetate (I) would almost certainly be hydrolysable in the animal body to free fluoroacetic acid, and that (II) and (III) would similarly give 2-fluoroethanol (oxidisable *in vivo* to fluoroacetic acid). These three compounds do, in fact, show toxicities of the same order as that of methyl fluoroacetate (or of fluoroacetic acid); (III) is, however, rather less toxic than might be expected.

The inactivity of the quaternary bromides is probably due to the inability of the body to rupture the C–N link in the $CH_2F{\cdot}CH_2{\cdot}\overset{+}{N}<$ grouping. The toxicity figures nevertheless reveal an interesting feature. For example, a saline solution of 2-fluorotetraethylammonium bromide injected subcutaneously into mice gave the following results: 500 mg./kg. killed 1/1 in 10 minutes; 400 mg./kg. 4/4 within 90 minutes; 300 mg./kg. killed 2/4 within 2½ hours, and 200 and 100 mg./kg. killed 0/4 and 0/1, respectively. These figures shows a very *rapid* action at the higher concentrations, and the toxicity was therefore probably due to the quaternary ammonium ion rather than to the 2-fluoroethyl group.

Discussion.—A wide variety of compounds containing the C–F link has been described in this and in previous parts and it is now convenient to classify them according to their physiological activity. In general, two types of assessment of animal toxicity* have been made: (*a*) by inhalation (liquids) and given as L.C. 50 in mg./l.; (*b*) by injection (liquids and solids) and given as L.D. 50 in mg./kg. of body weight.

Methyl fluoroacetate (MFA) has an L.C. 50 of 0·1 mg./l. for rabbits, guinea-pigs, and rats. The figure for fluoroethanol (FEA) is similar. For intravenous injection into rabbits MFA, FEA, and free fluoroacetic acid (a solid) have L.D. 50's of the order of 0·25 mg./kg., and for subcutaneous injection into mice the figure is about 6 mg./kg. for each substance. Thus any one of these three substances can be conveniently taken as a reference standard. The symptoms are the same in each case, the action being that of a convulsant poison with delayed action. In these compounds the fluorine is very unreactive chemically; for example, the fluorine atom in fluoroacetic acid is unaffected by water or aqueous alkali, and boiling alcoholic potassium hydroxide solution removed only 50% of the fluorine in 20 hours.

For purposes of comparison the magnitude of the toxicity of fluoroacetic acid is represented as *B*; *A* indicates higher toxicity (up to a factor of 2) and *C* indicates a lower toxicity (down to about ½ of that of fluoroacetic acid); *D* represents very low or negligible toxicity of the fluoroacetate type.

In class *B* are placed all simple esters $CH_2F{\cdot}CO_2R$ of fluoroacetic acid where R = Me, Et, Pr^n, Pr^i, Ph, etc. When substitution takes place in the α-hydrogen atoms, *e.g.* in methyl α-fluoropropionate or α-fluoro*iso*butyrate, then the compound is devoid of toxicity. This indicates the importance of the unsubstituted fluoromethyl group. In Part III (this vol., p. 912) it was shown that fluoroacetamide and a variety of substituted amides such as $CH_2F{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2Cl$ were, molecule for molecule, equally toxic with fluoroacetic acid and produced the same symptoms. The 2-chloroethyl group therefore contributed nothing appreciable to the toxicity of the molecule. The majority of the esters of fluoroethanol showed the toxicity of the parent alcohol; *e.g.*, 2-fluoroethyl chlorosulphonate, $CH_2F{\cdot}CH_2{\cdot}O{\cdot}SO_2Cl$, di-(2-fluoroethyl) sulphate and 2-fluoroethylglycine hydrochloride.

Fluoroacetaldehyde was as toxic as fluoroacetic acid.

All the toxic compounds mentioned above are either hydrolysable or oxidisable to fluoroacetic acid. In this connexion it should be noted that 1-chloro-2-fluoroethane was non-toxic. The chlorine atom in this compound was shown to be very unreactive chemically, hence hydrolysis to the toxic fluoroethanol in the animal body would be unlikely.

Compounds in which the fluorine atom is loosely bound are relatively non-toxic. Thus the COF group is not toxophoric as shown by the inactivity of acetyl fluoride, chloroacetyl fluoride, and ethyl fluoroformate. Also in the non-toxic class are the quaternary ammonium salts described in this paper, 2:2′-difluorodiethyl ethylene dithioglycol ether (Part IV, this vol., p. 916), was non-vesicant as well as non-toxic, whereas the corresponding chloro-compound is potent in both these respects. 2-Fluoroethyl sulphonyl chloride, $CH_2F{\cdot}CH_2{\cdot}SO_2Cl$, was also non-toxic by inhalation. These facts suggest that the body is unable to rupture the C–N and C–S bonds easily, and so the facile formation of fluoroethanol is prevented.

There is, however, another factor which must not be overlooked. In the highly toxic compounds the fluorine atom is firmly bound, and the toxic action may in some way be connected with this. In the compounds containing N or S in the 2-position to the F atom, the latter may

* See also Saunders and Stacey (*J.*, 1948, 697).

not be so firmly attached. There is some qualitative evidence to support this, but the matter requires further investigation.

The compounds in class *C* definitely show " fluoroacetate-like " activity, but are rather less potent than members of the standard class *B*.

2-Fluoroethyl fluoroacetate is a compound of outstanding toxicity (Part IV, *loc. cit.*). Its L.C. 50 for rabbits (inhalation) is 0·05 mg./l., *i.e.*, about half as great as for MFA. It is therefore placed in class *A*. Other factors apart from hydrolysis to fluoroethanol and fluoroacetic acid appear to be operative, and it seems that the molecule is toxic *per se*. The related fluoroacetylimino 2-fluoroethyl ether hydrochloride, $[CH_2F{\cdot}C(:NH_2){\cdot}O{\cdot}CH_2{\cdot}CH_2F]^+Cl^-$, was also placed in class *A*. This is understandable as it is readily hydrolysed by water to 2-fluoroethyl fluoroacetate. Other fluoroacetylimino ether hydrochlorides containing, however, only one fluorine atom fell into class *B*, as did also fluoroacetamidine hydrochloride itself.

Combination of " fluoroacetate " activity and certain other recognisable physiological effects have been successfully combined in fluoroaspirin (drugged sleep), triethyl-lead fluoroacetate (sternutation), difluoroethyl fluorophosphonate (miosis, but not powerful). In general, quaternary ammonium groups, and the $S{\cdot}CH_2{\cdot}CH_2Cl$ and $N{\cdot}CH_2{\cdot}CH_2Cl$ groups have not contributed anything to the potency of molecules containing them. Occasionally the $CH_2{\cdot}CH_2Cl$ group seems to have had some slight effect as in 2-chloroethyl fluoroacetate.

Apart from chemical considerations, purely physical phenomena, such as rate of diffusion through the cell membrane, must also play their part in determining the toxic action of a compound.

The following summarises the more important features of the above classification. The list is not exhaustive.

Class *A* : 2-Fluoroethyl fluoroacetate.

Class B^+ : 2-Chloroethyl fluoroacetate.

Class *B* : Fluoroacetic acids and salts, *e.g.*, sodium fluoroacetate, triethyl-lead fluoroacetate; all simple esters of fluoroacetic acid; fluoroacetamide and substituted amides; fluoroacetamidine hydrochloride; fluoroacetyl chloride and fluoride; fluoroethanol and its simple esters; fluoroacetaldehyde.

Class *C* : Fluoromethyl cyanide (but more toxic to rabbits); certain 2-fluoroethyl ethers; phenyl fluorothiolacetate, $CH_2F{\cdot}CO{\cdot}SEt$.

Class *D* : Esters of 1-alkylated fluoroacetic acids, $CHR'F{\cdot}CO_2R$ and $CR'R''F{\cdot}CO_2R$; acetyl and chloroacetyl fluoride; alkyl fluoroformates; quaternary ammonium salts, $CH_2F{\cdot}CH_2{\cdot}\overset{+}{N}R_3\overset{-}{X}$, chlorofluoroethane; sulphur-containing compounds, *e.g.*, $CH_2F{\cdot}CH_2{\cdot}SR$.

The synthesis will be described later of further highly toxic compounds containing the C–F link, which lend support to the views expressed above.

Experimental.

Ethyl Fluoroacetamidoacetate.—Glycine ethyl ester hydrochloride (2·8 g.) was dissolved in sodium carbonate solution (25 c.c. of 2N), fluoroacetyl chloride (1·94 g.) added, and the mixture shaken. After the evolution of carbon dioxide had ceased, the solution was carefully acidified with concentrated sulphuric acid (to avoid dilution). No precipitate was produced, so the mixture was extracted three times with ether (3 × 30 c.c.). The combined ethereal extracts were dried (Na_2SO_4), and the ether distilled off. The residue solidified on cooling in ice and salt and gave pale yellow crystals of the *ethyl* ester, m. p. 45—48°, which recrystallised from light petroleum (b. p. 40—60°) as white needle-shaped crystals (after seeding), m. p. 50—50·5°, soluble in water (Found : N, 8·62; F, 11·95. $C_6H_{10}O_3NF$ requires N, 8·94; F, 11·65%).

The condensation of glycine itself with fluoroacetyl chloride in the presence of alkali was attempted, but no derivative was isolated. Similarly fluoroacetic anhydride gave no derivative.

2-Fluoroethyl Aminoacetate Hydrochloride.—Glycine (7·5 g., 0·1 mol.) was added to fluoroethanol (37 g., 0·5 mol.), and the mixture heated under reflux while a stream of dry hydrogen chloride was passed through. After one hour all the glycine had disappeared, and after a further hour the product was cooled. The resultant mixture was extracted with alcohol–ether (1 : 2), leaving *2-fluoroethyl aminoacetate hydrochloride* as almost colourless crystals (12·9 g., 80%). After two recrystallisations from alcohol, the small colourless crystals had m. p. 150—150·5° (Found : N, 8·9; Cl, 22·8. $C_4H_9O_2NClF$ requires N, 8·86; Cl, 22·5%).

2-Fluoroethylbetaine Hydrochloride.—Anhydrous trimethylamine (12·2 g., 0·48 mol., 16 c.c.) and 2-fluoroethyl chloroacetate (29·5 g., 0·48 mol.) were mixed at the temperature of solid carbon dioxide–ether, and then allowed to warm to room temperature. Solid then began to separate and finally the mixture became quite warm. The solid was washed well with dry ether and filtered off. The *hydrochloride* was thus obtained as colourless hygroscopic crystals (36 g., 80%), m. p. 122° (Found : N, 6·8; Cl, 16·9. $C_7H_{15}O_2NClF$ requires N, 7·0; Cl, 17·7%).

Trimethyl-2-fluoroethylammonium Bromide.—Trimethylamine (11·8 g., 0·2 mol.) was mixed with bromofluoroethane (25·4 g., 0·2 mol.) at the temperature of a mixture of solid carbon dioxide and ether.

No reaction took place so the reagents were placed in a tube, sealed, and allowed to warm to room temperature. After 1½ hours' standing at room temperature much solid had separated. The tube was then opened, and the solid filtered off and washed with dry ether to remove pyridine and bromofluoroethane. The colourless crystalline *bromide* so obtained was pure, m. p. 244°; it contained fluorine and ionic bromine; yield 5·2 g. (14%) (this yield could probably have been increased on longer standing) (Found: N, 7·39; Br, 43·2. $C_8H_{13}NBrF$ requires N, 7·53; Br, 43·0%). The salt was readily soluble in water and fairly soluble in alcohol.

2-*Fluorotetraethylammonium Bromide*.—Triethylamine (10·1 g., 0·1 mol.) was heated under reflux with bromofluoroethane (12·7 g., 0·1 mol.) for 3 hours. The *bromide* which had separated was then filtered off and washed well with dry ether, being obtained as fine colourless cubes, m. p. 237° (4 g.) (Found: N, 5·92; Br, 35·1. $C_8H_{19}NBrF$ requires N, 6·14; Br, 35·1%.

2-*Fluoroethylpyridinium Bromide*.—Pyridine (7·9 g., 0·1 mol.) was heated under reflux with bromofluoroethane (12·7 g., 0·1 mol.) for 15 minutes; the product had then separated into two layers, and on cooling and scratching the lower layer crystallised. The crystals were filtered off, washed well with dry ether until free from pyridine and bromofluoroethane, and then dried in a vacuum. The *pyridinium bromide* (Found: N, 6·56; Br, 37·9. C_7H_9NBrF requires N, 6·79; Br, 38·9%) was obtained as colourless hygroscopic crystals, m. p. 180° (11 g., 53%). The compound contained fluorine.

Reaction between Bromofluoroethane and Dimethylaniline.—Anhydrous dimethylaniline (24·2 g., 0·2 mol.) was heated under reflux with anhydrous bromofluoroethane (25·4 g., 0·2 mol.). Solid began to separate after ¾ hour, and after 4¾ hours the solid present was filtered off and washed well with dry ether. The product thus obtained consisted of slightly hygroscopic, colourless, crystals (4 g.) which were recrystallised from aqueous alcohol. The compound (VI) was fluorine-free, contained ionic bromine, and had m. p. 199° (Hübner, Tölle, and Alhenstädt, *Annalen*, 1884, **224**, 346, give m. p. 200°) (Found: N, 6·8; Br, 37·6. Calc. for $C_{18}H_{36}N_2Br_2$: N, 6·5; Br, 37·2%).

3-*Carbethoxy*-N-2-*fluoroethylpyridinium Bromide*.—Ethyl nicotinate (2 g., 0·017 mol., prepared according to Engler, *Ber.*, 1894, **27**, 1787) was heated under reflux in an oil-bath with bromofluoroethane (2 g., 0·016 mol.) for 3 hours at 110°. The mixture had then become very viscous, but could not be crystallised from any organic solvent or water. On being left in a refrigerator, the viscous mass formed large cubic crystals.

The experiment was repeated with ethyl nicotinate (4 g., 0·032 mol.) and a large excess of bromofluoroethane (12 g., 0·1 mol.), the mixture being heated at 120° for 3 hours. The viscous reddish liquid which was formed was seeded with a few crystals from the preceding experiment and left at room temperature. After 2 days a reddish solid crystalline mass was formed. Some of the colour was removed by grinding the crystals (which were extremely hygroscopic) under acetone, and the *pyridinium bromide* was then dried in a vacuum desiccator over sulphuric acid; m. p. 86—88° (Found: Br, 28·9. $C_{10}H_{13}O_2NBrF$ requires Br, 28·8%). The *picrate* was prepared by adding a cold saturated solution of picric acid in alcohol to a concentrated alcoholic solution of the bromide. In a few minutes it began to crystallise in long yellow needles, which were filtered off, twice recrystallised from alcohol, and dried in a vacuum at 100° over phosphoric oxide; m. p. 128—129° (Found C, 44·7; H, 3·7; N, 13·46. $C_{16}H_{15}O_9N_4F$ requires C, 45·1; H, 3·52; N, 13·15%).

Attempted Condensation of Nicotinic Acid with Bromofluoroethane in Organic Solvents.—Nicotinic acid (1 g., 0·008 mol.) was dissolved in dioxan (5 c.c.), and bromofluoroethane (1 g., 0·008 mol.) added; the mixture was heated under reflux on an oil-bath for 3 hours, and the dioxan then removed on a water-pump, but the solid left in the reaction flask proved to be unchanged nicotinic acid. The procedure was repeated on the same scale with methanol and acetone as solvents, with similar results, and finally with bromofluoromethane in excess (10 g., 0·08 mol.) and without the addition of any solvent, but no condensation occurred under these conditions.

We are indebted to the Chief Scientist of the Ministry of Supply for permission to publish this paper. We are grateful to Dr. B. A. Kilby, Dr. J. P. O'Connor, and Mr. A. H. Carpenter for the majority of the toxicity determinations.

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278. *The Structures of Inorganic Oxy-acids: The Crystal Structure of Selenious Acid.*

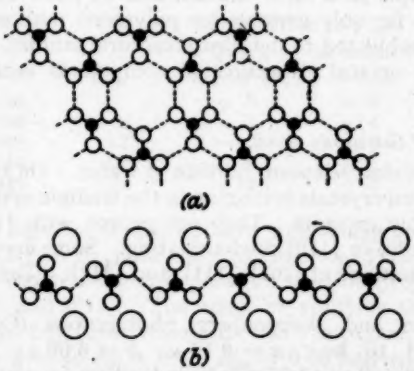
By A. F. WELLS and M. BAILEY.

The crystal structure of the orthorhombic form of selenious acid has been determined. The crystals are orthorhombic: $a = 9{\cdot}15$ A., $b = 6{\cdot}00$ A., $c = 5{\cdot}05$ A., space-group $P2_12_12_1$, 4 molecules in the unit cell. The structure consists of pyramidal SeO_3 groups (Se–O, 1·74 A. mean, and mean interbond angle 100°) joined by O–H–O bonds of length 2·56 A. and 2·60 A. There are four such bonds connecting each SeO_3 group to neighbouring groups. The structural schemes in other inorganic oxy-acids are briefly discussed.

THE crystal structures of inorganic oxy-acids H_mXO_n, which include compounds as important as sulphuric and nitric acids, have received very little attention. Only one such structure has been determined, that of the α-modification of iodic acid (Rogers and Helmholz, *J. Amer. Chem. Soc.*, 1941, **63**, 278). Compounds containing hydrogen and an electronegative

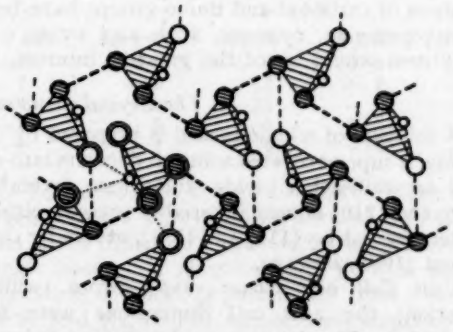
atom such as nitrogen, oxygen, or fluorine are of particular interest in view of the important part played by the hydrogen in binding together the molecules by means of hydrogen bonds. Rather more is known of the structures of three other groups of compounds closely related to the inorganic oxy-acids, *viz.*, hydroxy-acids [$B(OH)_3$, $Te(OH)_6$], metallic oxy-hydroxides (AlO·OH, FeO·OH), and acid salts (*e.g.*, $NaHCO_3$). An electron-diffraction study of nitric acid vapour shows that the free molecule should be represented as an oxy-hydroxy-compound ($OH·NO_2$), one N–O bond being appreciably longer than the other two (Maxwell and Mosley, *J. Chem. Physics*, 1940, **8**, 738). This will not, however, necessarily be the case in the crystal, which might consist of symmetrical NO_3^- ions held together by O–H–O bonds. If so, the extended hydrogen-bonded network of composition HNO_3, is to be compared with the infinite hydrogen-bonded $(HCO_3)_n^{n-}$ ion in $NaHCO_3$. In the acid salt KH_2PO_4 there is an infinite 3-dimensional array of PO_4^{3-} ions held together by hydrogen bonds, the K^+ ions being accommodated in the interstices of the $(H_2PO_4)_n^{n-}$ framework. The structure of crystalline H_2SO_4 may be closely related to this $(H_2PO_4)_n^{n-}$ framework.

FIG. 1.



Hydrogen-bond systems in (a) H_3BO_3 *and* (b) $NaHCO_3$.

FIG. 2.



The system of hydrogen bonds in α-HIO_3.

The crystal structures adopted by inorganic oxy-acids must depend on the part played by hydrogen in forming hydrogen bonds between the XO_n groups. In the acid salts so far studied there is at most one (short) O–H–O bond from any oxygen atom, and not all the oxygen atoms are necessarily engaged in hydrogen-bond formation. At the other extreme lie the hydroxy-acids, $X(OH)_n$, in crystals of which there are two (long) O–H–O bonds from every hydroxyl group, as in organic hydroxy-compounds such as resorcinol and pentaerythritol. It is convenient to classify the oxy-acids according to the ratio of H : O atoms, whereupon they fall into four groups :

H : O ratio =	1 : 4.	2 : 7.	1 : 3.	2 : 5.	1 : 2.	4 : 7.	2 : 3.	3 : 4.	1 : 1.
	HIO_4	$H_2S_2O_7$	HIO_3	H_2SO_5	H_2SO_4	$H_4P_2O_7$	H_2SeO_3	H_3PO_4	H_3BO_3
	$H_2S_2O_8$								H_6TeO_6
	(*a*)				(*b*)	(*c*)			(*d*)

In group (*d*) there are equal numbers of hydrogen and oxygen atoms, and every oxygen atom takes part in two (long) O–H–O bonds, as shown for boric acid in Fig. 1 (*a*).

In group (*b*) the ratio H : O is 1 : 2, *i.e.*, there could be one O–H–O bond to each oxygen atom as in the acid salts KH_2PO_4 and $(NH_4)_2H_3IO_6$, with the same H : O ratio. The remaining classes are more interesting. In (*a*), with H : O less than $\frac{1}{2}$, there are not enough hydrogen atoms to provide one O–H–O bond to each oxygen atom. One possibility would be that some of the oxygen atoms do not take part in the hydrogen-bonding scheme. For example, HIO_3 might form a chain structure like the $(HCO_3)_n^{n-}$ ion in sodium hydrogen carbonate (Fig. 1*b*). This acid is dimorphic, and the interatomic distances in the α-form have been interpreted as indicating the presence of " bifurcated hydrogen bonds " (Rogers and Helmholz, *loc. cit.*), four of which link each IO_3 group to neighbouring groups. There is, however, another interpretation of the " intermolecular " O–O distances (Wells, *Acta Crystallographica*, 1949, **2**, 128), according to which only half of those regarded by Rogers and Helmholz as hydrogen bonds should be regarded as O–H–O bonds. These are shown as heavy broken lines in Fig. 2, which shows a

projection of the structure of α-HIO_3 on one face of the orthorhombic cell. The IO_3 groups are then linked into infinite chains, as would be expected by analogy with the bicarbonate ion.

In group (*c*), with H : O ratio between ½ and 1, there are too many hydrogen atoms to allow only one O–H–O bond from each oxygen atom. If we assume that there will be, as in groups (*b*) and (*d*), one hydrogen bond for each hydrogen atom, then in H_2XO_3, for example, each XO_3 group will be attached to its neighbours by *four* such bonds. We have investigated the structure of one form of selenious acid (which is dimorphic) and find that this is the case. The hydrogen-bonding scheme is illustrated diagrammatically in Fig. 6.

A comprehensive discussion of the crystal structures of these oxy-acids cannot be attempted until the structures of more of the crystalline acids have been determined. It may be noted that other groups of hydrogen-bonded crystals present a similar problem to that of the oxy-acids. For example, in molecular crystals containing CO and NH groups the structural principles are comparatively simple if the molecule contains equal numbers of these groups, for each hydrogen atom joins together one carbonyl and one imino-group of different molecules. If, however, the molecule contains *different* numbers of carbonyl and imino-groups, then there are either too many or too few hydrogen atoms for any such simple structural scheme, and we have classes corresponding to (*a*) and (*c*) in the oxy-acids. So far only crystals (or polymers) with equal numbers of carbonyl and imino-groups have been subjected to detailed structural studies, *e.g.*, diketopiperazine, cyanuric acid, and nylon. The crystal structures of compounds such as oxalylurea would be of the greatest interest.

The Crystal Structure of Selenious Acid.

A solution of selenious acid is prepared by dissolving selenium dioxide in water. On rapid cooling, a supersaturated solution deposits lath-shaped crystals belonging to the triclinic system. Slow crystallisation yields (colourless) orthorhombic crystals. They are prisms with {100}, {110}, and {210} almost invariably present, either {100} or {110} predominating. Some crystals are terminated by {111} and {1$\bar{1}$1}, others by combinations of {101}, {111}, and {211}. There is a good (100) cleavage.

Unit Cell and Space-group.—From oscillation and Weissenberg photographs (Cu-K_α radiation) the unit cell dimensions were found to be: $a = 9{\cdot}15$ A., $b = 6{\cdot}00$ A., and $c = 5{\cdot}05$ A. The density was determined pyknometrically as 3·07 g./c.c., indicating 4 molecules in the unit cell. The only systematic absences are the odd orders of $h00$, $0k0$, and $00l$, whence the space-group is $P2_12_12$.

Determination of the Structure.—Apart from the hydrogen atoms, which cannot be located directly, there are 4 selenium and 12 oxygen atoms to place in the unit cell. All occupy general (4-fold) positions, the oxygen atoms in sets of four (designated O_1, O_2, and O_3). The approximate positions of the relatively heavy selenium atoms were readily obtained from the relative intensities of the high-order $hk0$ and $h0l$ reflexions, the oxygen scattering being neglected.

The relative intensities of the reflexions 10.1.0, 10.2.0, and 10.3.0, and of 840 and 740 suggested a value of x close to 0·205, while those of 170, 270, 370, and 470 showed that $0{\cdot}23 < y_{Se} < 0{\cdot}25$, or $0{\cdot}25 < y_{Se} < 0{\cdot}27$. The approximate parameters derived in this way were: $x_{Se} = 0{\cdot}205$, $y_{Se} = 0{\cdot}245$ (or 0·255), and $z_{Se} = 0{\cdot}11$. A decision was not necessary at this stage between the two possible values for y_{Se}, though when the oxygen atoms are inserted they correspond to different structures. Possible positions for oxygen atoms were found in the following way. Simplified structure factor graphs were made by plotting on a projection of the unit cell the lines along which the function $4 \cos hx \,.\, \cos ky$ or $-4 \sin hx \,.\, \sin ky$ (for $hk0$ reflexions) is zero, and indicating in which regions it has positive or negative values. From such graphs it is possible to see at a glance the approximate contribution of 4 oxygen atoms placed anywhere in the cell. For certain $hk0$ reflexions with appreciable structure amplitudes the selenium contribution was known to be small; these planes therefore require large contributions from the 12 oxygen atoms. Assuming only that three oxygen atoms will be within a distance of 2 A. of a selenium atom, forming a pyramidal group, only one orientation of the SeO_3 group gave reasonable agreement with these $hk0$ reflexions. This arrangement of oxygen atoms was consistent with a Patterson $h0l$ projection.

Calculations of F_{hk0} showed that the observed F's had a very much smaller range of values, from the strongest to the weakest spots, than the calculated F's, suggesting that the strong reflexions were appreciably reduced by extinction. The observed F_{hk0}'s were therefore placed on an approximately absolute scale and at the same time corrected for extinction by plotting the ratio of $I/I_{obs.}$ against I. Assuming a relation of the form $I_{obs.} = I/(1 + gI)$, the slope of the curve gives g, and the intercept on the $I/I_{obs.}$ axis gives the factor required to put the observed

values on an absolute scale. A value of $g = 0{\cdot}001$ was used. At this stage the agreement between calculated and observed F_{hk0} broke down for $h > 4$, and it was evidently necessary to alter y_{Se} from the value 0·25. A F_{hk0} projection incorporating about 40 terms was made, a strong artificial temperature factor being applied to the F's to eliminate the possibility of diffraction effects which might give false oxygen positions. (This also, of course, meant that the Se parameters were not known as accurately as if a longer series of F's had been employed, since the F's for planes of large θ are most sensitive to small variations in these parameters.) The approximate oxygen parameters determined in this way were:

	x.	*y*.	
O_1^2	0·10	0·35	(in this projection O_1 and O_2 are superposed).
O_3	$0{\cdot}15_5$	−0·05	

With these oxygen parameters it was possible to decide the direction of shift of F_{Se} from the value $\frac{1}{4}$, since for the $h40$ planes the sign of F_{Se} changes at $y = \frac{1}{4}$. The following figures show that y_{Se} must be taken between 0·24 and 0·245:

		Contribution to F_{h40}:			Total F.			
	$F_{obs.}$	Oxygen contribution.	Se contribution for: $y = 0{\cdot}24$.	$y = 0{\cdot}245$.	Se 0·24.	0·245.	0·255.	0·26.
140	—	+ 5	− 6	−3	− 1	+ 2	+ 8	+11
340	19	− 5	−14	−7	−19	−12	+ 2	+ 9
540	17	−12	−18	−9	−30	−21	− 3	+ 6
740	<2	+ 8	−14	−7	− 6	+ 1	+15	+22
940	—	+12	− 8	−4	+ 4	+ 8	+16	+20

The agreement was still not sufficiently good for $h50$ and $h60$. It was decided to make a F_{h0l} projection to check the *x* parameters of the oxygen atoms. This definitely showed that O_1 and O_2, which were superposed in the $hk0$ projection, have different *x* parameters (approximately 0·08 and 0·12). The effect of splitting the single (somewhat elliptical) $O_{1,2}$ peak in the $hk0$ projection into two atoms was then tried. Alteration of the $O_{1,2}$ parameters from $x = 0{\cdot}10$, $y = 0{\cdot}35$ to $x_{O_1} = 0{\cdot}12$, $x_{O_2} = 0{\cdot}08$ and $y_{O_1} = 0{\cdot}39$ and $y_{O_2} = 0{\cdot}31$ immediately improved the agreement for $h50$ and $h60$, as shown by the following figures. (These are given for $y_{Se} = 0{\cdot}243$, the value which appeared to give the best agreement).

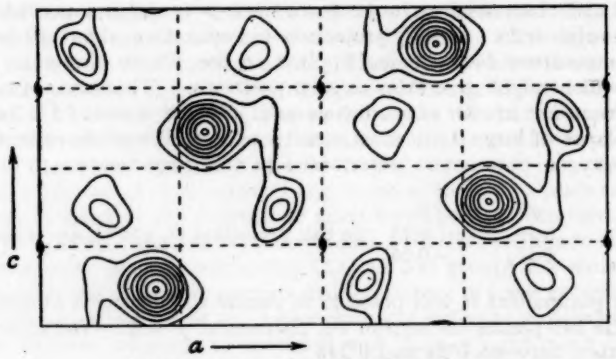
		O_1: *x* 0·10. O_2: *y* 0·35.	O_1: *x* 0·11, *y* 0·37. O_2: *x* 0·09, *y* 0·33.	O_1: *x* 0·12, *y* 0·39. O_2: *x* 0·08, *y* 0·31.
	$F_{obs.}$			
150	22	18	19	22·5
350	12	9·5	10·5	12·5
550	10	−0·5	−3·5	−10·5
750	4	−7	−6	−4
160	4	9·5	6·5	1
360	9	8	9	10
560	10	6·5	8·5	14·5
760	8	21	17	11

These *x* parameters also improved the agreement in the case of several pairs of $h0l$ reflexions, and it was now possible to prepare F_{hk0} and F_{h0l} projections utilising all the experimental data. For these projections a temperature factor of $e^{-2(\sin\theta/\lambda)^2}$ was applied since the series of observed F's was not considered sufficiently convergent. The final projections are shown in Figs. 3 and 4, and the parameters are:

	x.	*y*.	*z*.		*x*.	*y*.	*z*.
Se	0·205	0·243	0·115	O_2	0·08	0·31	−0·135
O_1	0·12	0·39	0·365	O_3	0·155	−0·04	0·133

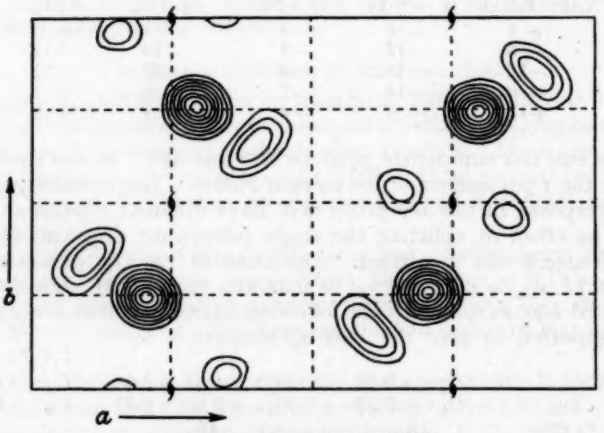
The least certain of these is the *z* parameter of O_3, which has not been determined directly since O_3 is nearly superposed on Se in the $h0l$ projection. This parameter was estimated by drawing a line through Se in the direction along which the Se peak is extended by O_3, assuming *x* for O_3 as deduced from the $hk0$ projection. Unfortunately, the $0kl$ projection is also valueless from this point of view as the atoms are practically superposed in pairs, O_2 on Se, and O_1 on O_3. Three-dimensional syntheses would give the position of O_3 more accurately, but since there appears to be no doubt about the hydrogen-bond system this extension of the work was not considered to be justified.

FIG. 3.



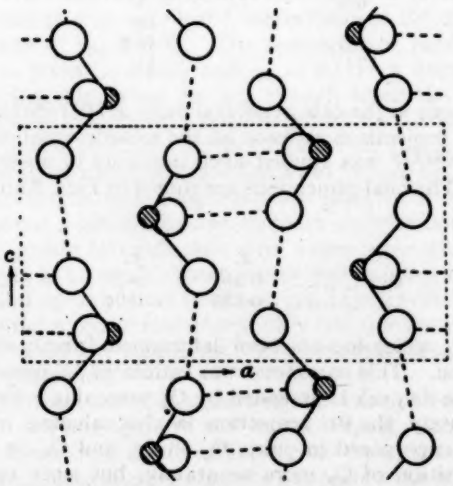
Fourier projection of H_2SeO_3 on (010).

FIG. 4.



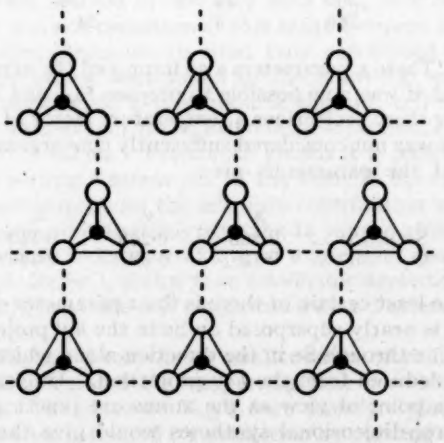
Fourier projection on (001).

FIG. 5.



Projection of the structure of H_2SeO_3 on (010).

FIG. 6.



The system of hydrogen bonds in H_2SeO_3 *(diagrammatic).*

The agreement between calculated and observed structure amplitudes is shown in the following table. The experimental data were obtained from Weissenberg photographs, the intensities being estimated visually, using the multiple-film method. The values of $F_{obs.}$ are the experimental values corrected for extinction as described above. It is considered that the data for the *hk*0 reflexions are the most reliable, as these were obtained from a thin needle of roughly square cross-section. The same extinction correction was applied to the data for the other zones. Absorption corrections, which would be more important for *h*0*l* and 0*kl* reflexions, have not been made.

Observed and Calculated Structure Amplitudes.

	F, obs.	F, calc.		F, obs.	F, calc.		F, obs.	F, calc.
200	77	− 94	060	50	− 57	101	35	+ 28
400	—	− 2	160	4	+ 4	201	55	+ 61
600	7	+ 5	260	50	+ 54	301	47	− 76
800	40	− 40	360	9	− 9	401	40	− 65
10.0.0	44	+ 55	460	29	− 27	501	43	+ 58
			560	10	+ 11	601	58	+ 66
110	12	+ 9	660	7	− 12	701	27	− 26
210	74	− 97	760	8	− 12	801	39	− 36
310	22	− 24				901	24	+ 26
410	54	+ 66	170	14	− 20	10.0.1	—	+ 3
510	12	− 11	270	31	+ 35	11.0.1	9	− 8
610	59	− 72	370	2	+ 8			
710	17	+ 18	470	45	− 55			
810	51	+ 66				102	94	− 88
910	—	+ 3				202	19	− 12
10.1.0	17	− 17	002	6	+ 8	302	95	+ 86
			004	90	−106	402	15	+ 6
020	86	−103	006	19	− 15	502	—	0
120	39	− 37				602	—	+ 4
220	66	+ 75	011	83	+ 88	702	35	− 46
320	20	+ 10	012	37	+ 54	802	—	− 6
420	44	− 44	013	41	− 49	902	35	+ 42
520	26	+ 30	014	12	− 5	10.0.2	8	+ 5
620	14	+ 7	015	24	− 58	11.0.2	26	− 46
720	4	− 7	016	13	− 18			
820	42	+ 47				103	25	+ 26
920	—	− 2	021	9	− 10	203	34	− 31
10.2.0	54	− 64	022	13	− 12	303	57	− 66
			023	8	− 8	403	33	+ 36
130	22	+ 18	024	58	+ 64	503	46	+ 61
230	51	+ 51	025	—	+ 4	603	30	− 45
330	33	+ 28	026	27	+ 22	703	34	− 36
430	76	− 79				803	20	+ 25
530	12	− 9	031	55	− 91	903	25	+ 26
630	71	+ 76	032	23	− 21	10.0.3	—	+ 3
730	—	− 11	033	39	+ 63			
830	44	− 43	034	—	0			
930	—	+ 4	035	45	+ 62	104	28	− 23
10.3.0	7	+ 10	036	12	+ 11	204	46	+ 56
						304	13	+ 6
040	68	+ 70	041	26	+ 27	404	13	− 8
140	—	− 1	042	15	+ 9	504	—	0
240	70	− 70	043	17	+ 23	604	—	− 6
340	19	+ 22	044	45	− 57	704	—	− 5
440	43	+ 39	045	14	− 20	804	23	+ 33
540	17	− 23				904	13	+ 11
640	13	+ 18	051	47	+ 27			
740	2	− 1	052	20	+ 18			
840	39	− 43	053	23	− 29	105	10	− 9
940	—	− 2	054	—	+ 3	205	29	− 36
10.4.0	33	+ 45	055	55	− 44	305	23	+ 30
						405	34	+ 51
150	22	+ 21	061	14	− 16	505	16	− 27
250	20	− 17	062	15	− 7	605	30	− 51
350	12	− 12	063	13	− 16	705	—	+ 11
450	59	+ 70	064	33	+ 51			
550	10	− 8				106	27	+ 49
650	64	− 68	071	32	− 37	206	15	+ 20
750	4	+ 5	072	11	− 22	306	23	− 44
850	29	+ 42	073	—	+ 10	406	9	− 10

Description of the Structure.—The structure consists of pyramidal SeO_3 groups joined together by hydrogen bonds to form double layers extending parallel to (100), the cleavage plane of the crystals. Fig. 5 shows a projection of the structure along the *b* axis, *i.e.*, viewed along a line lying in the plane of the layers. Within the SeO_3 group the bond lengths and interbond angles are: Se–O_1, 1·72 A., Se–O_2, 1·75 A., Se–O_3, 1·76 A.; O_1SeO_2, 97°, O_1SeO_3, 112°, and O_2SeO_3, 93° (mean about 100°). These may be compared with Se–O distances of 1·73 and 1·78 A. and interbond angles of 90° and 98° (2) in crystalline SeO_2 (McCullough, *J. Amer. Chem. Soc.*, 1937, **59**, 789). Distances between oxygen atoms within a SeO_3 group are: O_1O_2, 2·59 A., O_2O_3, 2·55 A., and O_3O_1, 2·89 A., and the shortest distances between oxygen atoms of different SeO_3 groups are: O_1O_2', 2·60 A., and O_1O_3', 2·56 A. These are the O–H–O bonds shown as broken lines in Figs. 5 and 6. The next shortest intermolecular O–O contact is O_3O_3', 3·12 A., followed by O_1O_3'', 3·21 A., O_1O_2'', 3·28 A., and O_3O_2', 3·51 A. The next nearest neighbours of a selenium atom are three more oxygen atoms at 3·00, 3·08, and 3·09 A., completing a distorted octahedron around Se. The system of hydrogen-bonding is best shown by a projection on (100), the plane of the layer, of the atoms in one double layer (Fig. 6). There are four O–H–O bonds connecting each SeO_3 group (ion) to its neighbours, their length being similar to that found in acid salts.

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279. *Acid–Base Catalysis in Non-aqueous Solvents. Part XII. The Amine-catalysed Decomposition of Nitramide in Anisole Solution.*

By R. P. BELL and A. F. TROTMAN-DICKENSON.

Kinetic measurements have been made on the decomposition of nitramide in anisole solution, catalysed by 24 amine bases. For a given type of amine (primary, secondary, or tertiary aniline derivative, or heterocyclic base) there is a relation between dissociation constants in water and catalytic constants in anisole, but no one relation holds for all four types. The distinction between primary, secondary, and tertiary aniline derivatives is attributed to anomalies in the dissociation constants in water, arising from hydrogen bonding between the amine cation and water molecules. Comparison with data in three other solvents indicates that the amine-catalysed decomposition of nitramide is favoured by an increase in dielectric constant.

IN addition to the large amount of work done with aqueous solutions, the kinetics of the decomposition of nitramide have been studied in *iso*amyl alcohol (Brönsted and Vance, *Z. physikal. Chem.*, 1933, *A*, **173**, 240) and in *m*-cresol (Brönsted, Nicholson, and Delbanco, *ibid.*, 1934, **169**, 379). The object of the present work was to extend the range of solvents studied, and to obtain more information about amine catalysts. Brönsted and Duus (*Z. physikal. Chem.*, 1925, **117**, 299) used substituted anilines as catalysts for the nitramide catalysis in water, and found a close relation between catalytic power and basic strength, but the few measurements reported for tertiary bases (Brönsted and Pedersen, *Z. physikal. Chem.*, 1924, **108**, 185; *J. Amer. Chem. Soc.*, 1938, **60**, 1513) do not conform to this relation. It is therefore of interest to investigate a wider range of amine bases, as has already been done for another type of reaction (Bell and Rybicka, *J.*, 1947, 24).

EXPERIMENTAL.

Anisole was dried ($CaCl_2$) and fractionated, the middle fraction boiling over a range of 0·5° being used. Nitramide was prepared by the method of Marlies, LaMer, and Greenspan (*Inorg. Synth.*, Vol. I, p. 68, New York, 1939), and could be stored in an open vessel over potassium hydroxide in a vacuum desiccator. Some samples which had been stored over phosphoric oxide gave low and erratic velocity constants, presumably because of some volatile acidic impurity. It was often more convenient to store the nitramide in the ice-box as an approximately 0·1M. solution in anisole, the half-life being then about 60 days. The bases used as catalysts were (if liquid) dried with potassium hydroxide, and were purified by fractional distillation or recrystallisation. Their physical constants are given in the tables of results.

The reaction was followed by measuring the pressure of nitrous oxide evolved in the apparatus shown in Figure 1, designed by Mr. E. F. Caldin. Its total volume is about 20 c.c. and it holds 3 c.c. of solution. The vertical capillary is of 1-mm. internal diameter, is graduated in millimetres, and is evacuated at the top. With these dimensions, 3 c.c. of a 0·1M-nitramide solution give a pressure change of about 120 mm. of mercury. The whole apparatus is held in a clamp below the surface of a thermostat at 25° ± 0·01°, and agitated by an electrically operated rubber hammer which strikes the bulb about 80 times per minute (cf. Bell and Baughan, *Proc. Roy. Soc.*, 1937, **158**, *A*, 464). To carry out an experiment, the nitramide and catalyst solution are mixed outside the apparatus and then run into the bulb. The

apparatus is evacuated through *A* for a few seconds, then sealed off at *B*, and placed in its clamp in the thermostat. It was possible to obtain reliable readings about two minutes after agitation had commenced, *i.e.*, about four minutes after mixing. Readings were then taken at suitable intervals, and the end-point observed after at least eight half-lives. For some of the slower reactions, completion of the reaction was accelerated by immersing the apparatus in a thermostat at 60°, and then returning it to the 25° thermostat to observe the end-point.

The velocity constants were obtained graphically by plotting $\log_{10}(r_0 - r)$ (where r is the manometer reading) against the time, and are defined by $k = \mathrm{d}\log_{10}(r_0 - r)/\mathrm{d}t$ with t in minutes. The plots obtained showed a very slight curvature as the reaction progressed, owing to a displacement of the equilibrium, $H_2N_3O_2^- + B \rightleftharpoons (HN_3O_2)^- + BH^+$, where B is the basic catalyst; however, all experiments were carried out with approximately the same nitramide concentration and covered about the first three quarters of the reaction, so that the best straight lines gave comparable values for the velocity constants in different experiments. The existence of this equilibrium also caused the apparent catalytic constant k/c to vary slightly with the base concentration, c, making it necessary to use an extrapolation to obtain the true catalytic constant. Let the concentration of $(B + BH^+)$ be c, and the concentration of $(HN + N^-)$ (N = nitramide) be x; similarly, let the concentrations of both BH^+ and

TABLE I.

c = concentration of base in moles/kg. of solution.
k = first-order velocity constant, decadic logarithms, minutes.

Quinoline, b. p. 231—233°,	10^3c	13·4	27·1	30·1	39·6	62·1
$k_c = 0{\cdot}365$.	k/c	0·487	0·440	0·463	0·437	0·442
Pyridine, b. p. 114·6—114·8°,	10^3c	6·12	15·9	19·5	29·7	
$k_c = 0{\cdot}814$.	k/c	0·850	0·829	0·832	0·833	
*iso*Quinoline, b. p. 239·4—239·6°,	10^3c	4·18	16·7	24·2	29·3	51·8
m. p. 22·5°, $k_c = 1{\cdot}14$.	k/c	1·29	1·23	1·20	1·21	1·17
α-Picoline, b. p. 128·3—128·5°,	10^3c	1·64	2·32	6·50	9·26	
$k_c = 2{\cdot}22$.	k/c	2·52	2·44	2·36	2·34	
γ-Picoline, b. p. 144·2—144·6°,	10^3c	1·67	3·38	6·75	10·1	
$k_c = 2{\cdot}30$.	k/c	3·19	3·05	2·83	2·60	
β-Picoline, b. p. 141·5—141·8°,	10^3c	3·36	7·37	10·34		
$k_c = 2{\cdot}94$.	k/c	2·71	2·82	2·80		
2 : 4-Lutidine, b. p. 155·3—155·4°,	10^3c	1·59	2·91	3·88	5·75	
$k_c = 8{\cdot}00$.	k/c	6·40	6·76	6·90	7·22	
s-Collidine, b. p. 172—173°,	10^3c	0·84	1·87	2·64	3·20	
$k_c = 13{\cdot}5$.	k/c	9·2	10·2	11·1	11·6	
Dimethylaniline, b. p. 191·0—	10^3c	13·1	70·0	86·8	203	254
191·2°, $k_c = 0{\cdot}065$.	k/c	0·100	0·0814	0·0758	0·0745	0·0767
	10^3c	261	396	404	616	
	k/c	0·0754	0·0713	0·0731	0·0692	
Dimethyl-*m*-toluidine, b. p. 208·5—	10^3c	158	252	309		
209·0°, $k_c = 0{\cdot}089$.	k/c	0·099	0·096	0·096		
Dimethyl-*o*-toluidine, b. p. 182·4—	10^3c	175	233	643		
182·7°, $k_c = 0{\cdot}115$.	k/c	0·125	0·123	0·120		
Dimethyl-*p*-toluidine, b. p. 207·0—	10^3c	20·7	48·8	73·3	103	
207·7°, $k_c = 0{\cdot}260$.	k/c	0·291	0·293	0·280	0·257	
Diethylaniline, b. p. 211·1—211·4°,	10^3c	15·3	32·9	58·5	90·1	
$k_c = 0{\cdot}360$.	k/c	0·371	0·377	0·370	0·363	
Diethyl-*p*-toluidine, b. p. 102—	10^3c	3·30	6·03	14·5	27·0	
103°/14 mm., $k_c = 1{\cdot}30$.	k/c	1·52	1·69	1·47	1·36	
Benzyldiethylamine, b. p. 207·2—	10^3c	0·28	1·23	1·49	2·22	2·82
207·8°, $k_H = 7{\cdot}8$.	k/c	8·1	10·6	10·9	12·1	12·8
	10^3c	3·85	4·10	4·30		
	k/c	15·4	16·2	15·7		
Tri-*n*-butylamine, b. p. 209·2—	10^3c	0·83	1·61	2·05	3·10	3·95
210·2°, $k_H = 5{\cdot}5$.	k/c	6·4	7·5	8·1	11·9	17·2
Triethylamine, b. p. 88·1—88·4°,	$10^3/c$	0·91	1·44	2·84	4·13	
$k_H = 5{\cdot}1$.	k/c	5·19	5·09	4·97	5·20	
Methylaniline, b. p. 193·3—	10^3c	270	376	730		
193·5°, $k_c = 0{\cdot}0122$*.	k/c	0·0124	0·0131	0·0133		
Ethyl-*o*-toluidine, b.p. 212·7—	10^3c	202	267	381	650	
212·8°, $k_c = 0{\cdot}0149$*.	k/c	0·0150	0·0153	0·0155	0·0157	
Ethylaniline, b. p. 202·0—202·2°,	10^3c	222	346	501	728	
$k_c = 0{\cdot}0230$*.	k/c	0·0228	0·0239	0·0232	0·0232	
o-Chloroaniline, b. p. 206·0—	10^3c	624	954	1220		
206·3°, $k_c = 0{\cdot}000230$*.	k/c	0·000234	0·000252	0·000270		
m-Chloroaniline, b. p. 103°/14	10^3c	252	513	840		
mm., $k_c = 0{\cdot}00078$*.	k/c	0·00076	0·00074	0·00072		
p-Chloroaniline, m. p. 69·2—	10^3c	261	522	742	744	
69·3°, $k_c = 0{\cdot}00147$*.	k/c	0·00140	0·00133	0·00126	0·00128	
Aniline, b. p. 181·5—181·9°,	10^3c	381	654	857	1023	
$k_c = 0{\cdot}00350$*.	k/c	0·00505	0·00650	0·00693	0·00770	

N^- be y. Then, if k_e and k_N are the catalytic constants of B and N^-, respectively, in decadic logarithms, the actual reaction velocity is given by

$$0{\cdot}434v = k_e(x - y)(c - y) + k_N y(x - y) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Most of the bases used are considerably weaker than the nitramide ion, and it can therefore be assumed that y is much smaller than c or x, and terms in y^2 can be neglected. Under the same conditions, we can write $y = (K'cx)^{\frac{1}{2}}$, where K' is the equilibrium constant for the reaction, $HN + B \rightleftharpoons N^- + BH^+$. The observed value of k/c is then given by

$$k/c = 0{\cdot}434v/cx = k_e + \{k_N - k_e(1 + c/x)\}(K'x/c)^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Since the variation of k/c with c is small, and the initial nitramide concentration was kept approximately the same throughout, equation (2) can be applied to the mean velocity constants obtained graphically. For most purposes, k_e can be obtained by plotting k/c against $c^{-\frac{1}{2}}$ and extrapolating to $c^{-\frac{1}{2}} = 0$, since for the stronger bases $c \ll x$ throughout, whilst for the weaker bases $k_N \gg k_e$; in either case, the expression inside the first bracket is effectively independent of c. This method of extrapolation was used for the majority of the bases studied. For the weakest bases used, the extent of reaction with nitramide will be very small, but the high concentrations of base may well involve an appreciable medium effect. Equation (2) would not then be applicable, and in fact, for some of these bases, k/c increases slightly with increasing c, which is the opposite change to that predicted by the equation. In such cases we have allowed for the medium effect by plotting k/c against c and extrapolating to $c = 0$; catalytic constants obtained by this method are marked with an asterisk in Table I. The general conclusions drawn from the catalytic constants would not be modified by any reasonable change in the method of extrapolation.

The data for the three bases benzyldiethylamine, tri-*n*-butylamine, and triethylamine cannot be treated in this way, since they are strong enough to react with nitramide to a considerable extent, so that the observed catalysis is largely due to the nitramide ion, especially in dilute solutions of the bases. In equation (1) we can now put $y \sim c$, giving

$$k/c = k_N + (k_e/K' - k_N)c/x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

It should thus be possible to obtain k_N by plotting k/c against c and extrapolating to $c = 0$. The resulting values are given in Table I; those from the data for tri-*n*-butylamine and triethylamine agree well, whilst benzyldiethylamine gives a somewhat higher value, probably because it is not a strong enough base for the successful application of equation (3). It is not possible to derive values of k_e for these bases without a knowledge of the equilibrium constants K' in anisole solution.

Nitramide decomposes slowly in pure anisole, the velocity constant being about 5×10^{-6}. This rate could be neglected in most of the amine solutions, but a small correction was made in the experiments with *o*- and *m*-chloroaniline. It was thought possible that the water produced in the reaction might catalyse the reaction; however, the spontaneous rate was not appreciably increased by using anisole saturated with water, and three experiments with diethyl-*p*-toluidine solutions containing 0·04 mol. of water per l. gave normal velocity constants.

Results.—The results of the kinetic measurements are collected in Table I.

Discussion.

The measurements given above show that the decomposition of nitramide in anisole solution is a first-order reaction catalysed by bases, as in the other solvents previously investigated. It is of interest to compare the catalytic powers of the bases studied with their basic strengths in water, and the latter are most conveniently expressed by pK_a, the acid dissociation exponent of the conjugate acid cations, BH^+. This quantity is more convenient than the conventional basic dissociation constant K_b, since K_a is normally the quantity which is measured experimentally, K_b being derived from it by using the ionic product K_w, which varies considerably with temperature and salt concentration. Table II contains the collected values of the catalytic constants, k_e, together with pK_a and the sources of the latter.

Figure 2 shows a plot of $\log_{10} K_e$ against pK_a for all the amines considered above. It is clear that there is no single relation between basic strength and catalytic power which covers all the catalysts studied, but that such a relation is satisfied (probably within the uncertainty of the experimental values) for each of the four classes of amines given in Table II. The equations of the four lines drawn in Figure 1 are as follows:

Primary aromatic amines	$K_e = 4{\cdot}1 \times 10^{-4}(1/K_a)^{0{\cdot}44}$
Secondary ,, ...	$K_e = 1{\cdot}1 \times 10^{-5}(1/K_a)^{0{\cdot}44}$
Tertiary ,, ...	$K_e = 3{\cdot}8 \times 10^{-5}(1/K_a)^{0{\cdot}44}$
,, heterocyclic amines	$K_e = 3{\cdot}2 \times 10^{-4}(1/K_a)^{0{\cdot}44}$

The separation of the amines into four distinct classes seems too marked to be ascribed entirely to modifications in the shape of the potential energy curves (cf. Horiuti and Polanyi, *Acta Physicochim. U.R.S.S.*, 1935, **2**, 505; Bell, *Proc. Roy. Soc.*, 1936, *A*, **154**, 414), since the differences are comparable with those caused by a change in the charge-type of the catalyst, and the slopes of the four lines are identical. A similar distinction between primary, secondary, and tertiary amines has been observed in this laboratory in catalysed keto–enol transformations,

TABLE II.

	$\log_{10}k_c$.	pK_a.	Source.
Pyridine and quinoline bases.			
Quinoline	1·56	4·80	(1)
Pyridine	1·91	5·27	(2)—(7)
*iso*Quinoline	0·11	5·36	(8)
α-Picoline	0·35	6·02	(7)
γ-Picoline	0·36	6·00	(9)
β-Picoline	0·47	6·00	(9)
2 : 4-Lutidine	0·90	6·65	(8)
s-Collidine	1·13	7·34	(2), (4)
Tertiary aromatic amines.			
Dimethylaniline	$\bar{2}$·81	5·06	(10)
Dimethyl-*m*-toluidine	$\bar{2}$·95	5·34	,,
Dimethyl-*o*-toluidine	$\bar{1}$·06	5·50	,,
Dimethyl-*p*-toluidine	$\bar{1}$·42	5·86	,,
Diethylaniline	$\bar{1}$·56	6·56	,,
Diethyl-*p*-toluidine	0·11	7·90	,,
Secondary aromatic amines.			
Methylaniline	$\bar{2}$·08	4·78	,,
Ethyl-*o*-toluidine	$\bar{2}$·17	4·92	,,
Ethylaniline	$\bar{2}$·36	5·11	,,
Primary aromatic amines.			
o-Chloroaniline	$\bar{4}$·30	2·77	,,
m-Chloroaniline	$\bar{4}$·89	3·52	,,
p-Chloroaniline	$\bar{3}$·17	4·00	,,
Aniline	3·54	4·58	,,

References for pK_a *values.* (1) Felsing and Biggs, *J. Amer. Chem. Soc.*, 1933, **55**, 3624. (2) Goldschmidt and Salcher, *Z. physikal. Chem.*, 1899, **29**, 89. (3) Hahn and Klockmann, *ibid.*, 1904, **48**, 435. (4) Lunden, *J. Chim. physique*, 1907, **5**, 574. (5) Mizutani, *Z. physikal. Chem.*, 1926, **118**, 327. (6) Hall, *J. Amer. Chem. Soc.*, 1930, **52**, 5115. (7) Guzman-Barron, *J. Biol. Chem.*, 1937, **121**, 313. (8) Karrer and Schmid, *Helv. Chim. Acta*, 1946, **29**, 1853. (9) Constam and White, *Amer. Chem. J.*, 1903, **29**, 36. (10) Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.

FIG. 1.

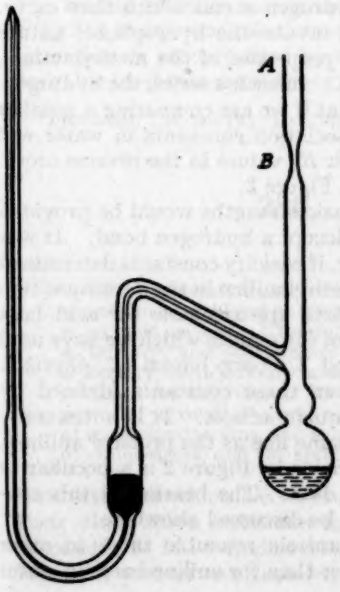
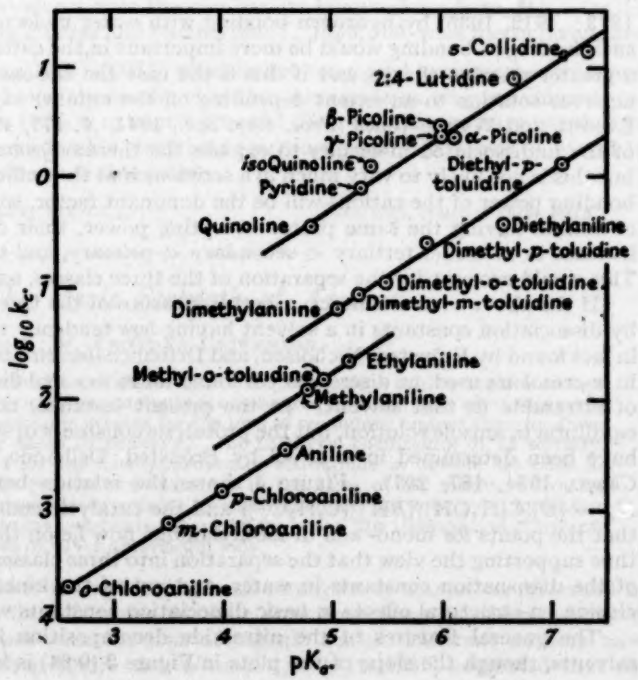


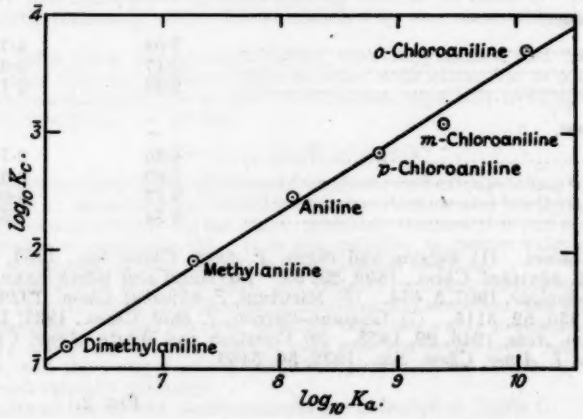
FIG. 2.



and the data of Brönsted, Nicholson, and Delbanco (*Z. physikal. Chem.*, 1934, **169**, 379) on the decomposition of nitramide in *m*-cresol solution show that mono- and di-methylaniline diverge considerably from the relation which holds for primary aniline derivatives when dissociation constants in water are used as the basis of comparison. A part of the differences between primary, secondary, and tertiary amines might be statistical in character, arising from the different numbers of hydrogen atoms on their cations; however, calculation shows that not more than a 50% difference between primary and tertiary amines could be accounted for on this basis, and it is in any case doubtful whether hydrogen atoms attached to the same central atom should be considered statistically independent (cf. Brönsted, *Chem. Reviews*, 1928, **5**, 322).

In our opinion, the failure of primary, secondary, and tertiary bases to conform to the same relation between K_c and K_a can be attributed to anomalies in the dissociation constants in water, which may not represent correctly the proton-accepting powers of the three classes of base. It has long been realised that the dissociation constants of the aliphatic amines are not simply related to their structures, and attempts have been made to explain these anomalies in terms of differing degrees of hydration of the amine molecules (cf. Moore and Winmill, *J.*, 1907,

FIG. 3.



1373; 1912, 1635) by hydrogen bonding with water molecules. However, it seems likely that such hydrogen bonding would be more important in the cations, where the hydrogen atoms have a greater positive charge, and if this is the case the cations of the amines will be stabilised in aqueous solution to an extent depending on the number of hydrogen atoms which they carry. Everett and Wynne-Jones (*Proc. Roy. Soc.*, 1941, *A*, **177**, 499) invoke the hydrophobic nature of the undissociated molecules to explain the thermodynamic properties of the methylamines, but this is not likely to vary much in a series such as the anilines. In such a series, the hydrogen-bonding power of the cations will be the dominant factor, so that if we are comparing a number of amines having the same proton-accepting power, their dissociation constants in water will increase in the order tertiary < secondary < primary, and their K_a values in the reverse order. This would account for the separation of the three classes, as in Figure 2.

If the above view is correct, a better measure of the true basic strengths would be provided by dissociation constants in a solvent having less tendency to accept a hydrogen bond. It was in fact found by Brönsted, Nicholson, and Delbanco (*loc. cit.*) that, if basicity constants determined in *m*-cresol are used, no discrepancy is found for mono- and di-methylaniline in the decomposition of nitramide in that solvent. In the present instance, no data are available for acid–base equilibria in anisole solution, but the protolysis constants of six of the amines which we have used have been determined in *m*-cresol by Brönsted, Delbanco, and Tovborg-Jensen (*Z. physikal. Chem.*, 1934, **167**, 207). Figure 3 shows the relation between these constants (defined by $K_A = [B][C_7H_7OH]/[BH^+][C_7H_7O^-]$) and the catalytic constants in anisole. It is noteworthy that the points for mono- and di-methylaniline now lie on the same line as the primary anilines, thus supporting the view that the separation into three classes shown by Figure 2 is a peculiarity of the dissociation constants in water, and not of the kinetic data. The bearing of this conclusion on structural effects in basic dissociation constants will be discussed elsewhere.

The general features of the nitramide decomposition in anisole resemble those in other solvents, though the slope of the plots in Figure 2 (0·64) is lower than for aniline bases in water

(0·80), *iso*amyl alcohol (0·92) and *m*-cresol (0·84). It is of interest to compare the absolute rates of the reaction in different solvents. Table III gives the catalytic constants for aniline in the four solvents, the values in water and anisole being converted into those for 20°, assuming an activation energy of 20 k.-cals./mole (cf. Bell and Baughan, *Proc. Roy. Soc.*, 1937, *A*, **158**, 464).

TABLE III.

Catalytic constants for aniline at 20° (log_{10}, *minutes*).

Solvent.	Water.	*m*-Cresol.	*iso*Amyl alcohol.	Anisole.
K_c	0·97	0·15	0·033	0·0019
Dielectric constant	80	13	5·7	4·4

It will be seen that the rate decreases with decreasing dielectric constant, as would be expected for a reaction between two uncharged molecules, in which the transition state presumably involves a considerable charge separation.

The approximate value of 6 obtained for the catalytic constant of the nitramide ion in anisole is about 100 times as great as that of a primary aromatic amine having the same dissociation constant in water. The data for other solvents suggest (cf. Bell, "Acid–Base Catalysis," Oxford, 1941, p. 112) that this ratio would be at least 2000 for a carboxylate ion of similar strength. The nitramide ion thus has an abnormally small catalytic effect, just as in aqueous solution, in which its catalytic constant was found by Tong and Olson (*J. Amer. Chem. Soc.*, 1941, **63**, 3406) to be about 30 times smaller than that of a carboxylate ion of the same dissociation constant. The values given represent upper limits, since in each case a possible decomposition of the nitramide ion itself has been neglected.

These considerations have some bearing on the structure of the nitramide molecule, about which there is still some doubt. It is usually written $NH_2{\cdot}NO_2$, as originally suggested by Thiele and Lachmann (*Annalen*, 1895, **288**, 267). However, Hantzsch (*ibid.*, 1896, **292**, 340) maintained for many years that it was a stereoisomer of hyponitrous acid, HON:NOH, but eventually abandoned this structure in favour of NH:NO·OH (*Ber.*, 1930, **63**, 1270) in view of optical evidence on the structure of the ion of phenylnitroamine (Cambi and Szego, *ibid.*, 1928, **61**, 2081). The structure of the ion does not necessarily correspond with that of the undissociated molecule, and Pedersen (*J. Physical Chem.*, 1934, **38**, 581) interpreted the mechanism of decomposition by supposing that the equilibrium, $NH_2{\cdot}NO_2 \rightleftharpoons HN{:}NO{\cdot}OH$, is set up in aqueous solution, with $NH_2{\cdot}NO_2$ predominating; on the other hand, Kortüm and Finckh (*Z. physikal. Chem.*, 1940, **48**, *B*, 32) concluded from optical evidence that the equilibrium favoured the form, HN:NO·OH. Measurements of dipole moments by Hunter and Partington (*J.*, 1933, 309) were inconclusive, and these authors favoured the structure, $\overset{-}{N}{=}\overset{+}{N}(OH)_2$, which is not supported by any other evidence. The kinetic evidence mentioned above favours the view that nitramide exists predominantly as $NH_2{\cdot}NO_2$ in aqueous solution, since the low catalytic effect of the nitramide ion suggests that its formation is accompanied by a considerable electronic rearrangement. However, it would be desirable to obtain more direct evidence on this point.

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280. *The Basic Strength of Amines.*

By A. F. TROTMAN-DICKENSON.

It is suggested that greater solvation of amine ions than free amines makes the amine ions appear more stable when their dissociation constants are measured in water than when measured in an inert solvent. The stabilisation is greater for the ions of secondary amines than for those of tertiary, and still greater for those of primary. The catalytic coefficients of 13 tertiary, secondary, and primary anilines for the decomposition of nitroamide in anisole are cited as evidence for this view. Its consequences are examined in the cases of the relative solvating power of solvents, the neutralisation of nitroethane by methylamines, the entropy of ionisation of methylamine ions, the substituent constants for aromatic bases, the dissociation constants of amino-acids, and the stabilities of silver amminium ions.

THE attempts which have been made to explain the basic strengths of amines, as measured by their dissociation constants in water, in terms of their structures have not been nearly as successful as have similar attempts with the ions of organic acids. Different authors have favoured various explanations; thus Moore and Winmill (*J.*, 1912, 1635) suggested that the

amines were hydrated, Hammett ("Physical Organic Chemistry," New York 1940, p. 225) proposed a proximity effect, Brown (*Science*, **1946**, **103**, 385) a steric effect, and Palit (*J. Phys. Coll. Chem.*, **1947**, **51**, 1028) a "polarstriction effect." Here the suggestion is made that much confusion has been caused by the fact that the argument has centred around the aqueous ionisation constants of the amines, and that an allowance must be made for the solvation, and consequent stabilisation, of the amine ions.

The catalytic coefficients of aniline bases for the decomposition of nitroamide in anisole were found by Bell and Trotman-Dickenson (preceding paper) not to be related to their dissociation constants by one simple Brönsted equation. However, each class of amines obeys a separate equation, as follows:

Tertiary amine	$K_c = 3{\cdot}8 \times 10^{-5}\ (1/K_B)^{0{\cdot}64}$
Secondary amine	$K_c = 1{\cdot}1 \times 10^{-5}\ (1/K_B)^{0{\cdot}64}$
Primary amine	$K_c = 4{\cdot}1 \times 10^{-6}\ (1/K_B)^{0{\cdot}64}$

where K_c is the catalytic coefficient expressed in decadic logarithms and reciprocal minutes, and K_B is the dissociation constant of the aniline ion in water at 25°.

Since the tertiary amines are the best catalysts, it is very unlikely that steric factors are responsible for this separation, as they would be expected to act in the opposite way.

Potential-energy curves have been used (Horiuti and Polanyi, *Acta Phys. Chem. U.R.S.S.*, **1935**, **2**, 505; Bell, *Proc. Roy. Soc.*, **1936**, **154**, *A*, 414) to provide a physical picture of the Brönsted relation. The separation of the anilines into different classes might be ascribed to the alteration in the shapes of the potential-energy curves; but this would involve a change in the value of the Brönsted exponent, whereas within the limits of experimental error it is 0·64 in each case. The value of the other constant in each equation would probably be altered at the same time.

In Fig. 2 of Bell and Trotman-Dickenson's paper (*loc. cit.*) the logarithms of the catalytic coefficients of dimethylaniline, methylaniline, and four nuclear-substituted anilines in anisole are plotted against the logarithms of their dissociation constants in *m*-cresol. These are the only six bases for which the data are available. The dissociation constants in *m*-cresol were determined by Brönsted, Delbanco, and Tovborg-Jensen (*Z. physikal. Chem.*, **1934**, **169**, 207) and are defined by the relation

$$K_m = [B][C_7H_7OH]/[BH^+][C_7H_7O^-].$$

One straight line is obtained of slope 0·64 despite the amines being drawn from each of the three classes. It may be noted that Brönsted, Nicholson, and Delbanco (*ibid.*, **1934**, **169**, 379) found that the values of the catalytic coefficients of methylaniline and dimethylaniline for the decomposition of nitroamide in *m*-cresol did not obey the same relation as the primary anilines, if they used aqueous dissociation constants, but did if they used those determined in *m*-cresol. Brönsted and Pedersen (*ibid.*, **1924**, **108**, 185) also found that the three tertiary and heterocyclic bases which they studied as catalysts for the decomposition of nitroamide in aqueous solution did not obey the same relation as the primary anilines, using aqueous dissociation constants; the magnitude of the separation appears to be smaller than in anisole, perhaps indicating some specific interaction of the solvent with the transition state.

These considerations indicate that the cause of the classification is to be found in the use of aqueous dissociation constants. The dissociation process of an amine ion can be represented:

$$NR_3H^+ + H_2O \rightleftharpoons H_3O^+ + NR_3$$

where R is either hydrogen or a substituent. The constant for this dissociation process will be used for the dissociation constant of the amine in this paper unless otherwise stated. It has the advantages of representing a symmetrical process and of being the usual constant determined experimentally; the basic dissociation constant being calculated by using a value for the ionic product of water.

The rate-determining step in basic catalysis by an amine may be represented as:

$$SH + NR_3 \longrightarrow S\text{–}H\text{–}NR_3$$

where SH is the substrate and S–H–NR_3 represents the transition state, for which no satisfactory conventional electronic formula can be written. The transition state subsequently yields NHR_3^+ and S which undergoes further reaction. The stability of the free amine ion is not involved, but only that of the amine. The stability of solute species can be increased by solvation, which with water and many other solvents may be regarded as taking place by a

hydrogen-bonding mechanism. The water molecule and the hydroxonium ion in aqueous solution are normally regarded as the standards for dissociation-constant measurements in water, so for the purposes of this argument their relative solvation can be neglected. Both the amine and the amine ion will be solvated to some extent, but the hydrogen bonding between the amine ion and the water will probably be much stronger, as suggested by Huggins (*J. Org. Chem.*, 1936, **1**, 407) and Pauling ("Nature of the Chemical Bond," Ithaca, 1940, p. 287). The types of bonding are essentially different; the bonding between an amine and a hydroxylic solvent takes place through the hydrogen atom supplied by the solvent, as shown by the use of deuterated solvents (Gordy, *J. Chem. Physics*, 1939, **7**, 93). Indeed this is the only type possible for a tertiary amine. In the case of the ion, the hydrogen in the bond will be one of those originally on the nitrogen atom.

Now a secondary and a tertiary amine whose proton-accepting capacity in an inert solvent are the same may be considered. In water or other hydroxylic solvent the amines will be slightly stabilised owing to solvation, but the ions will be stabilised much more, thus lowering their dissociation constants. Because the ion of the secondary amine carries one more hydrogen atom than that of the tertiary amine, the ion of the secondary amine has greater capacity for forming hydrogen bonds, and consequently will be the more stabilised. For this reason, the ratio of the dissociation constants measured in hydrogen-bonding solvents will not be a suitable measure of the proton-accepting powers of the amines when considered as catalysts among different classes of amines, though it will be quite suitable when, say, only tertiary amines are studied. The catalytic powers of the amines can better be compared with the dissociation constants of their ions in solvents such as *m*-cresol where hydrogen bonding with the ion cannot take place. Dissociation constants in water will represent the secondary bases as being too strong in comparison with the tertiary amines. Similar arguments can be applied to the primary amines.

Gordy (*loc. cit.*) has found that the hydrogen-bonding power of the amines is proportional to the logarithm of their basic dissociation constants. If the bonding between water and the free amines were appreciable, this would lead to the Brönsted relations for the different classes of amine having different exponents, which within the limits of experimental error is not so.

In a hydrogen-bonding solvent the ions of primary amines will be more solvated than those of secondary amines, which in turn will be more solvated than those of tertiary amines. Those solvents which will solvate most strongly are those with oxygen atoms carrying some negative charge; on structural grounds a list of solvents in order of decreasing solvating power is: ethyl alcohol, methyl alcohol, water, *m*-cresol, and anisole. Comparison of the absolute values of dissociation constants of electrolytes in different solvents does not directly reveal their relative solvating powers, because other factors, such as dielectric constant, affect the degree of dissociation. Since the kinetic data show that amine ions are very little solvated in *m*-cresol (Brönsted, Nicholson, and Delbanco, *loc. cit.*), and we have seen that the kinetic data in anisole fit a Brönsted relation based on dissociation constants in *m*-cresol, *m*-cresol will be taken as a convenient example of an "ideal" solvent in which very little hydrogen bonding with the amine ions takes place. It is convenient also to regard tertiary amines as a norm, and to express the stabilisation of other ions in terms of them. The stabilisation can be estimated from the dissociation constants in *m*-cresol, which the kinetic data in anisole show to be applicable in anisole also. The dissociation constants for the amine ions in *m*-cresol for which direct measurements have not been made can readily be found from the kinetic data. The stabilisation is best expressed as that correction which must be applied to the negative logarithms of the aqueous dissociation constants of the secondary and primary anilinium ions in order that a plot of the negative logarithms of the constants in water and *m*-cresol will give a line of unit slope. The corrections are $-0{\cdot}83$ pK_B units for secondary amines and $-1{\cdot}50$ for primary amines. From the measurements of the dissociation constants of amine ions in ethyl and methyl alcohols (Larrson, *Z. physikal. Chem.*, 1934, **169**, 207; Goldschmidt and Matthiesen, *ibid.*, 1926, **119**, 439), similar corrections for use with dissociation constants measured in these solvents can be found. They are $-1{\cdot}63$ for secondary and $-2{\cdot}29$ for primary bases in ethyl alcohol, and $-1{\cdot}48$ for secondary and $-2{\cdot}07$ for primary bases in methyl alcohol. The magnitude of these corrections is in agreement with the hydrogen-bonding capacity of the solvents predicted on structural grounds.

There is very little experimental kinetic data on amines which can be used to check these corrections, as the data for the mutarotation of glucose and decomposition of nitramide in water are not sufficiently extensive. One case is the neutralisation of nitroethane by ammonia and methylamines (Pearson, *J. Amer. Chem. Soc.*, 1948, **70**, 204) in water. The data, which are

given in the following table, relate to the velocity of the reaction at 0° and 5·2°, but an extrapolation using the activation energy may be made to 25°.

Base.	log K_B.	Correction.	log K_B corr.	log k_{25} (obs.).	log k_{25} (calc.).
Trimethylamine	$\bar{5}$·80	0	$\bar{5}$·80	1·56	1·55
Dimethylamine	$\bar{4}$·78	−0·83	$\bar{5}$·95	1·64	1·65
Methylamine	$\bar{4}$·62	−1·50	$\bar{5}$·12	1·08	1·08
Ammonia	$\bar{5}$·22	—	—	$\bar{1}$·84	—

log K_B is the logarithm of the dissociation constant of the base in water at 25°, the correction is the one found above for water, log K_B corr. is the corrected value for the dissociation constant, k_{25} (obs.) is the velocity constant for the reaction:

$$CH_3{\cdot}CH_2{\cdot}NO_2 + B \longrightarrow C_2H_4NO_2^- + BH^+$$

expressed in l./mol.-minute at 25°, and log k(calc.) is the logarithm of the velocity constant calculated from the equation

$$k_{25} = 1{\cdot}93 \times 10^4 (K_B \text{ corr.})^{0{\cdot}67}.$$

This equation represents the best line that can be drawn through the three points obtained by plotting log k_{25} against log K_B corr. By an extrapolation the logarithm of the corrected dissociation constant of ammonia is found to be $\bar{7}$·27; this represents a correction of −1·95 units which is of the order that would be expected from an extrapolation of the corrections for the primary and seconday amines.

Since the entropy of a system may be regarded as a measure of the degree of order existing in that system, the entropy of ionisation of substances will be affected by the degree of solvation of the ions. The hydroxonium ion in water is believed to be strongly solvated, and the amine ion will undergo hydrogen bonding with water molecules though perhaps not to the same extent as the hydroxonium ion; comparatively, the difference between the solvation of the free water molecule and the amine will be small. The dissociation of the amine ion will therefore involve a negative entropy change corresponding to a transition to a state of greater order. The less the amine ion is hydrogen bonded the greater will be the negative entropy change of ionisation. As the hydrogen bonding is greater where there is the larger number of hydrogen atoms in the amine ion, the following gradation of entropy changes can be drawn up:

$$\Delta S_{NH_4^+} > \Delta S_{NMeH_3^+} > \Delta S_{NMe_2H_2^+} > \Delta S_{NMe_3H^+}$$

Everett and Wynne-Jones (*Trans. Faraday Soc.*, 1939, **35**, 1380) found

Acid.	ΔS (cals./mol./degree).
Ammonium ion	− 0·54
Methylammonium ion	− 4·7
Dimethylammonium ion	− 9·5
Trimethylammonium ion	−15·3

However, the values of ΔC_p, if interpreted in terms of hydrogen bonding, lead to results in direct contradiction to those deduced from entropy changes. Other, as yet unknown, factors must be involved.

It has been observed by Hall and Sprinkle (*J. Amer. Chem. Soc.*, 1932, **54**, 3469) that para-substitution of a methyl group in aniline to form *p*-toluidine is accompanied by an increase in basic strength in water of 0·48 pK_B unit, where pK_B is the negative logarithm of the acid dissociation constant; but *N*-substitution to give *N*-methylaniline increases the basic strength by only 0·23 pK_B unit. It is strange that substitution on the active part of the molecule should produce the smaller change. This may be due to the fact that *N*-substitution involves two conflicting effects: (*a*) an increase in basic strength due to the inductive effect of the substituent, (*b*) a decrease in basic strength due to the replacement of a hydrogen atom on the nitrogen by a non-bonding group. The magnitude of the second effect is the correction involved for a change from a primary to a secondary amine or from a secondary to tertiary, that is 0·67 or 0·83 pK_B unit respectively. These corrections when applied to the aniline methylaniline change give 0·90 pK_B unit as the substituent constant for a methyl group on the nitrogen atom. If these corrections are applied to all the available data on aromatic amines, it is found that, when the first and second substituents are the same group, the second produced a far greater change in the pK_B of the amine, the ratio being 1 : 1·8.

The difference in the solvation of amines with different numbers of hydrogen atoms on the nitrogen provides an explanation of the reversal in order of strength of amine bases, judged by their dissociation constants, which has been observed, in passing from measurements in water

to measurements in ethyl alcohol. From the corrections for the comparison of secondary amines with tertiary amines in the different solvents, it can be seen that such a reversal of apparent strength will occur for any tertiary amine within $-1{\cdot}63 + 0{\cdot}83 = -0{\cdot}80$ pK_H units in water of a secondary base. Such a reversal is observed with methyl-*n*-propylaniline and ethylaniline (Hall and Sprinkle, *loc. cit.*).

Branch and Calvin (" Theory of Organic Chemistry," New York, 1941, p. 229) have pointed out that the aqueous acid dissociation constants of the *N*-substituted glycines provide evidence of the hydrogen bonding of the hydrogen atoms on the positively charged nitrogen atom with the water molecules. It would be expected that *N*-methyl substitution would increase the basic strength because of the stabilisation of the positive change, but this effect is more than counteracted by the reduction in stabilisation by hydrogen bonding. The dissociation constants are from Cohn and Edsall (" Proteins, Amino Acids, and Peptides," New York, 1943, p. 85).

Acid.	pK_a.	Acid.	pK_a.
$H_3\overset{+}{N}\cdot CH_2\cdot CO_2H$	2·34	$(CH_3)_2\overset{+}{N}H\cdot CH_2\cdot CO_2H$	1·94
$CH_3\cdot\overset{+}{N}H_2\cdot CH_2\cdot CO_2H$	2·23	$(CH_3)_3\overset{+}{N}\cdot CH_2\cdot CO_2H$	1·84

Several workers (Larrson, *loc. cit.*; Britton and Williams, *J.*, 1935, 796; Bruehlman and Verhoek, *J. Amer. Chem. Soc.*, 1948, **70**, 1401) have measured the dissociation constants of the ions $(AgAm)^+$ and $(AgAm_2)^+$ in water, where Am represents an amine molecule. If the logarithms of the dissociation constants of the silver amminium ions are plotted against the logarithms of the dissociation constants of the amine ions, the points for the different classes of amines lie on three separate straight lines. This would be expected, because the silver amminium ion of the tertiary amine cannot be stabilised by hydrogen bonding, as it has no hydrogen atoms attached to the nitrogen. Hence the ions formed with the tertiary amines are the least stable. The silver amminium ions of the primary amines are the most stable; those of the secondary amines are intermediate, as would be expected.

Much more work is required both on the catalytic effect of amines and upon their dissociation constants in non-bonding solvents. Results of dissociation-constant measurements on two secondary and three tertiary amines in benzene by Davis and Schuhmann (*J. Res. Nat. Bur. Stand.*, 1947, **39**, 221) show separation into types similar to that found in *m*-cresol, but the results are not sufficiently extensive to gauge the magnitude of the effect.

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281. *Studies on Some Metal Electrodes. Part VI. The Arsenic Electrode as a Metal–Metal Oxide–Oxygen Electrode.*

By A. RIAD TOURKY and A. A. MOUSA.

By examining massive arsenic electrodes in buffers of different pH in air, it is found that, although the straight portions of the pH–potential curves obtained are almost parallel to the line representing the variation of the hydrogen electrode potential with pH, yet they are characterised by E_0' values approximately 0·1 volt more positive than that theoretically derived for the $As–As_2O_3$ system. A value approaching the theoretical one is only obtained on using electrode systems involving the powdered metal. It is shown by experiment that the shift in potential cannot be ascribed to the nature of the deposited metal, to the participation of some higher oxides in the electrode equilibrium, or to alloy formation between arsenic and platinum when the latter is used as substrate. The possibilty of explaining such abnormally high positive potentials in terms of concentration polarisation is also excluded. A valid explanation is that the massive arsenic electrode is governed by an oxygen overvoltage effect and, like the antimony electrode, behaves as a metal–metal oxide–oxygen rather than as a metal–metal oxide electrode.

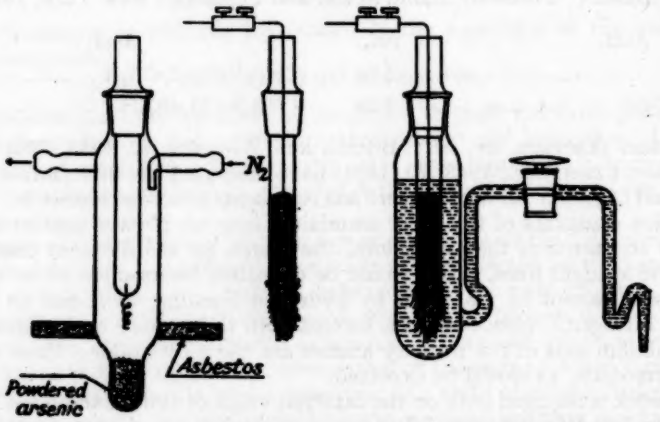
IT has been shown in Parts III, IV, V (*J.*, 1948, 752, 756, 759) that the behaviour of the antimony electrode in air can be satisfactorily accounted for in the light of the modern theory of lattice defects as applied to the oxide formed on the metal. Owing to the impermeability of the initially formed film to oxygen molecules and to the non-diffusion through it of the metal ions towards the solid–gas interphase, a layer of oxygen doublets persists on the electrode surface leading

to an overvoltage effect of about 0·1 volt which is superposed on the thermodynamic potential. By subjecting the electrode alternately to hydrogen and to high vacuum, the layer of oxygen is removed and the behaviour of the electrode is governed only by the trioxide. In the present investigation results of measurements with arsenic electrodes of different types and under a variety of conditions are recorded which not only substantiate the theory previously outlined but indicate that the arsenic electrode, not yet adequately studied, is better than the antimony electrode for measuring pH.

Experimental.

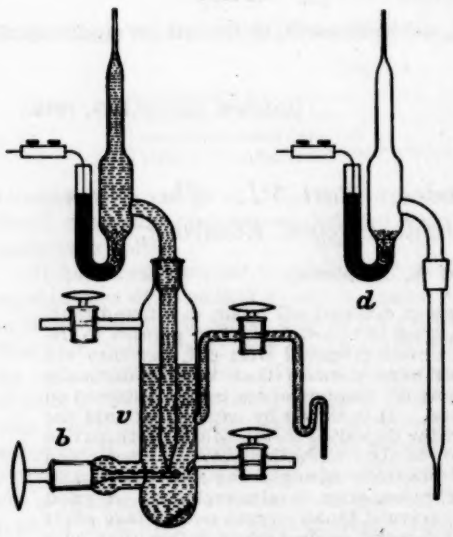
Preparation of Metallic Arsenic.—The standard state of arsenic is the solid metallic α-form. There are also the yellow, cubic, low-density γ-form and some varieties formerly regarded as amorphous, but

Fig. 1.



now known (Cohen and Olie, *Z. physikal. Chem.*, 1910, **71**, 1) to be solid solutions of the other two forms. In the present investigation, only α-arsenic was used; it was prepared by reduction of pure arsenious oxide with sugar-charcoal in an atmosphere of carbon dioxide (cf. Lenan *et al.*, *Phil. Mag.*, 1928, **6**, 666). The metal was powdered and resublimed in portions in pure nitrogen in especially devised columns at ~350°, a temperature high enough to cause the irreversible transformation of any unstable forms into the stable one (Stöhr, *Z. anorg. Chem.*, 1939, **242**, 44, 138). The metal, which was deposited in glistering clusters, left no residue after sublimation. The inlet and outlet for nitrogen were then sealed off while the gas was circulating so as to minimise oxidation of the element pending its use.

Fig. 2.



Electrodes.—These consisted of the freshly prepared massive or powdered metal, singly or in conjunction with each other, and with or without the stable octahedral or the unstable vitreous form of arsenious oxide. Fig. 1 shows how electrodes of the massive metal are prepared by sublimation and employed. Fig. 2 represents a device for electrodes made of the powdered metal with or without the oxide. It consists of the part *v* to hold the buffer, which should be presaturated with the oxide when this is used, and the part *d* to contain the powdered material. By gentle tapping, the powder can be well packed round a platinum spiral sealed into the U-tube and serving as lead to the mercury contact. After being evacuated and sealed off at its upper and its lower end, *d* is fitted tightly into *v* with its capillary end passing through *b*, which when turned serves to break the seal and thus to fill *d*. The forms of the oxide used were prepared as described in Part VIII (this vol., p. 1305). The buffer solutions were prepared and the measurements performed as in previous parts of this series (*loc. cit.*).

Results and Discussion.

Series A: Electrodes consisting of the Massive Metal.—Types of electrode. Freshly prepared massive electrodes obtained by sublimation and deposition on platinum, the deposit being renewed

before each set of measurements in any one buffer, are referred to as type A_I, and A_{II} represents electrodes prepared as above but left to age in air for *ca.* 12 months.

Electrodes of the type A_I set up potentials which were very sensitive to changes in pH. Comparison of the initial values obtained after ~30 minutes in each buffer with those obtained after ~70 hours shows that, up to pH 7, there is but a slight tendency in almost all buffers to acquire less positive values with time. Above pH 7, the final potentials are always more positive than the initial ones. By plotting the initial and final potentials against pH, curves representing straight lines within the approximate pH ranges 3—10 and 4—9, respectively, are obtained (see Fig. 3). The E_0' values calculated in each case are 0·3399 and 0·3320 volt and are thus about 0·1 volt more positive than the reversible one (see below).

Electrodes of type A_{II} behave similarly, but the final potentials on the whole are less positive than the corresponding ones of A_I. The reproducibility of the pH ranges as well as the relations representing the straight lines are, however, less definite with these electrodes than with the other type or with systems involving the oxide.

Series B : Electrodes consisting of the Massive Metal in Conjunction with Arsenious Oxide.—Types of electrode. B_I and B_{II} represent freshly prepared massive electrodes in conjunction with the stable octahedral and with the vitreous form of the oxide, respectively.

The tendency of these electrodes to acquire, with time, less positive potentials below, and more positive ones above, pH 7 is much more marked than with electrodes of the former types. The potentials on the alkaline side of pH 7 fall more nearly on the straight lines after longer immersion periods. The pH–potential curves constructed on the basis of either initial or final potentials are again straight lines, but in this instance only within the approximate pH range 4—7, above which they flatten.

Electrodes of the type B_{II} show analogous behaviour save for the greater extent of flattening of the pH-potential curves above pH 7. The E_0' values obtained with both types of electrode approach very closely those obtained with electrodes of the A types.

Series C : Electrodes involving the Powdered Metal.—Types of electrode. Type C_I represents electrodes consisting of the powdered metal only, and C_{II} those consisting of both powder and massive metal; C_{III} and C_{IV} are the same as C_I and C_{II}, respectively, but with the octahedral oxide.

The potentials set up with these types of electrode on immersion are on the whole about 0·1 volt less than those set up by electrodes of series A or B in the corresponding buffer solutions. The initial and final potentials in particular with electrodes involving the oxide were very close to each other and showed but slight variation with time. By plotting both initial and final values with electrodes of the types C_I and C_{II} against pH, straight lines are not obtained, though the best straight line would divide the points into sets lying slightly above or below it on the acid and the alkaline side of about pH 7, respectively, and coincides fairly closely with the theoretical plot for the As–As_2O_3 system. By plotting the potentials obtained after 30 minutes with electrodes of the types C_{III} and C_{IV} against pH, straight lines within the approximate pH range 1—7 are obtained with E_0' values closely approaching the thermodynamic one. Above pH 7, all curves tend to flatten towards more positive values as with all types of electrode involving the oxide. Fig. 3 shows the pH–potential plots obtained with the different types of electrode.

One of us (A. A. M.) will report elsewhere how, in the light of the above and other studies, the freshly deposited arsenic electrode, not hitherto used, may with advantage replace the antimony electrode for determining pH, and in Part VIII, on the basis of the amphoteric and other properties of arsenious trioxide, we interpret the pH–potential plots. For elucidating the theory underlying the functioning of the electrode it remains, however, necessary to ascertain that the lower E_0' value actually represents the thermodynamic one and that the higher values can only be attributed to the oxygen over-voltage effect operating on the massive electrodes.

(A) *The Thermodynamic Potentials of the* As–As_2O_3 *and the* As–As_2O_5 *System.*—It has been suggested that in the presence of oxygen and moisture, arsenic is superficially transformed into the trioxide. There is, however, the possibility that the pentoxide as well might be formed, and the two electrode reactions may be represented, respectively, by

$$2As + 6OH' = As_2O_3 + 3H_2O + 6e \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$2As + 10OH' = As_2O_5 + 5H_2O + 10e \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

From a knowledge of the free energy of formation of each of the reactants and resultants, the net free-energy change ΔF of each of the above reactions and hence the reversible potentials of each of the electrode systems As–As_2O_3 and As–As_2O_5 may be computed.

The free energy of formation of As_2O_3 at 35° as computed from the relation $\Delta F = \Delta H - T\Delta S$ is 137,457 cals. when ΔH is taken equal to 156,400 cals. ("High-temperature Specific Heat Equations for Inorganic Substances," *Bur. Mines Bull.*, 1934, p. 371) and ΔS equal to 64·73. For calculating the latter value, entropy values at 298·1° K. for arsenious oxide, oxygen, and elementary arsenic of 25·6, 49·03, and 8·40, respectively, were used, which by integration between 298·1° and 308·1° K. yield the values 26·41, 29·27, and 8·61, respectively. The free energy of formation of water and the hydroxyl ion at 35° can be derived from the relations:

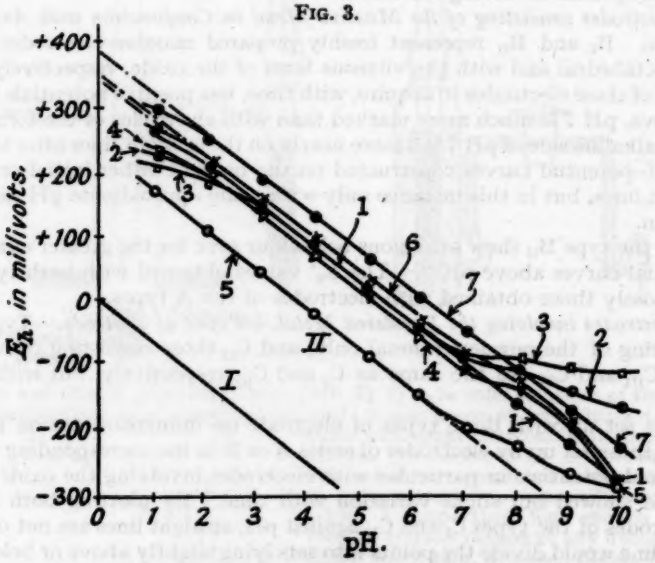
$$H_2 + \tfrac{1}{2}O_2 = H_2O;\ \Delta F = 56{,}560 \text{ cals. at } 25° \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and

$$H_2O = H^+ + OH^-;\ \Delta F = -19{,}105 \text{ cals. at } 25° \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The free energy of reaction (3) at 35° as computed from the oxygen–hydrogen cell, given by Nernst and Wartenberg as $1·232 - 0·00085(t - 17)$ volts, is 56,143 cals. That of reaction (4)

FIG. 3.



(1) *Freshly deposited massive electrode at* 35° *(no oxide).*
(2) *Same, but with the octahedral oxide.*
(3) ,, ,, *vitreous* ,,
(4) *Electrode after* 11 *months' ageing.*
(5) *Electrodes involving powdered metal.*
(6) *Fresh massive electrode under oxygen atmosphere.*
(7) ,, ,, *at* 20°.

I.—*Reversible hydrogen electrode system.* II.—*Reversible* As–As_2O_3 *system.*

is found to be −19,278 cals. at 35°, as calculated from the relation, $\log K_w = -RT \log K_w$, where K_w, the ionic product of water at 35°, is obtained from Harned and Hammer's relation (*J. Amer. Chem. Soc.*, 1933, **55**, 2194), $\log K_w = -4787/T - 7·1321 \log T - 0·010365T + 22·801$, applicable between 0° and 60°. By combining equations (3) and (4), the free energy of the hydroxyl ion at 35° is found to be 36,865 cals.

When arsenic is in its standard state, its free energy of formation is zero. Accordingly, ΔF of reaction (1) is 83,696 cals., and the reversible potential of the electrode system As–As_2O_3 is −0·605 v. The potential of the hydrogen electrode in a solution containing hydroxyl ions at unit activity, computed as shown above from the reaction $H^+ + OH^- = H_2O + e$, is +0·836 v. The difference in potentials denoting the magnitude of the term E_0' of the As–As_2O_3 system is therefore 0·231 v. at 35°.

By proceeding in an analogous manner, 218,300 cals. being taken as the value for the heat of formation of As_2O_5 (de Passille, *Ann. Chim.*, 1936, **5**, 83), the E_0' term of the As–As_2O_5 system is found to be 0·425 v. at 35°. The former value agrees very closely with those registered with electrodes involving the powdered metal (type C) and are about 0·1 volt less than those obtained with electrodes of the types A or B.

(B) *The Effect of Other Factors on the Positive Shift observed with Massive Electrodes.*—(i) *Nature of the deposited metal and possible alloy-formation.* By examining the behaviour of a large arsenic crystal on the one hand and of the deposited metal on the other in a buffer solution of pH 3, Gatty and Spooner (" Electrode Potential Behaviour of Corroding Metals," Oxford, 1938, p. 367) attributed the higher positive potentials observed by Kruger and Kahlenberg (*Trans. Amer. Electrochem. Soc.*, 1930, **58**, 341) than those obtained by Schuhmann (*J. Amer. Chem. Soc.*, 1924, **46**, 1444) to the variable state of the metal and to local action processes on the electrode surface. As this conclusion could only be justified if measurements were made at pH values leading to a linear pH–potential plot, single crystals prepared as recommended by those authors were examined throughout the whole pH range, whereby it was found that they behave in the same manner as electrodes of type A_I. Analogously, it was found that the positive shift could not be ascribed to alloy formation between arsenic and the platinum substrate, since deposition on copper, nickel, or steel did not show any peculiar behaviour that would indicate alloy formation, at least under the conditions prevailing during deposition. Alloy formation with platinum only occurs at *ca.* 600° (Friedrick and Leroux, *Mettallurgie*, 1908, **5**, 148), an arsenide with an average content of 87·04% Pt being formed. With this alloy, the pH–potential curve was an almost straight line denoting an E_0' value equal to about 0·800 v. as compared with the value of 0·980 v. reported by Furman (*J. Amer. Chem. Soc.*, 1922, **44**, 2685) for the potential of bare platinum in aerated aqueous solutions.

(ii) *Participation of higher oxides.* The fact that the E_0' values obtained with arsenic electrodes of the massive type lie between those of the $As–As_2O_3$ and of the $As–As_2O_5$ system might indicate at first sight that the electrodic behaviour is governed by a mixture of both oxides. This, however, cannot be the case, since the potentials set up with aged electrodes were found to be less positive than those obtained with fresh ones, whereas the former should be richer in the higher oxide. Further, since the E_0' values obtained with massive electrodes of different types fluctuate only within narrow limits, it is difficult to assume the presence of a definite ratio of both oxides. The same observation also excludes the possibility of attributing the shift to concentration polarisation of any type.

(iii) *Effect of the prevailing atmosphere.* Electrodes of the type A_I were examined in atmospheres of hydrogen, nitrogen, and oxygen, and the last, unlike the other two gases, had a profound effect on the electrode (see Fig. 3). This justified regarding the electrode as a metal–metal oxide–oxygen electrode, the potential of which is affected by the prevailing oxygen pressure, so that the cathodic process $O_2 + 2H_2O + 4e = 4OH^-$ is favoured by higher partial pressures. This view is further supported by the fact that the potentials are considerably dependent on temperature. For instance, measurements at 20° and 35° showed a positive shift of *ca.* 100 and 140 mv., respectively, which corresponds satisfactorily to the value of $\Delta E/\Delta t = 2{\cdot}7$ mv./degree often observed in overvoltage phenomena. Since $\Delta E/\Delta t$ for reversible electrodes is usually very small, the effect may be directly ascribed to the absorbed film of oxygen doublets with its movable oxygen atoms which possess volume properties and thus respond to variations in temperature.

(iv) *Effect of cathodic and anodic polarisation.* Massive arsenic electrodes were either cathodically or anodically polarised in 0·1N-sulphuric acid till visible bubbles of hydrogen or oxygen formed on their surface. The results indicated that neither process had a noticeable effect on the electrodic behaviour manifested without polarisation. The rapid formation of a surface oxide film even after cathodic polarisation is the result of the great tendency of the metal to become oxidised and explains satisfactorily why, after immersion, the massive arsenic, in contradistinction from the antimony electrodes (*J.*, 1948, 752, 756), show steady-state potentials not appreciably changing with time. Arsenic differs also from tungsten which, after anodic polarisation, was found not to respond to variations in pH. This may be ascribed to the circumstance that, unlike the latter, the anodic dissolution of the metal is not totally inhibited so that the released metal ions and the hydroxyl ions in the solution form a secondary oxide on the electrode.

Conclusions.—In the light of the above results, the ideas previously developed to interpret the behaviour of the massive antimony electrode may be applied to freshly deposited arsenic electrodes, and these also can be considered as metal–metal oxide–oxygen rather than metal–metal oxide electrodes. In both cases the persistence of oxygen doublets on the electrode surface is imposed by the impermeability of the oxide film to oxygen molecules and by the non-diffusion through it of metal ions towards the solid–gas interface. Although the theory of lattice defects has only been applied to phenomena occurring at about 1000°, when the reactants involved are at " thermodynamic equilibrium," the behaviour of arsenic and antimony, as compared with

that of copper when functioning as a metal–metal oxide electrode, provides evidence for the applicability of the theory to oxidation reactions occurring at room temperature and opens new fields of inquiry into the phenomenon of passivation in general.

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282. *Studies on Some Metal Electrodes. Part VII. The Behaviour of Arsenic Electrodes prepared by Sublimation and Decomposition of Arsine out of Contact with Air.*

By A. RIAD TOURKY and A. A. MOUSA.

Electrodes prepared by sublimation of arsenic or decomposing arsine in an atmosphere of pure hydrogen are found to behave similarly to each other. The potential–pH curves initially obtained bear considerable analogy to those found in air with massive electrodes with the difference, however, that the overvoltage effect decayed within a few hours, whereby the thermodynamic potentials were ultimately obtained. This remarkable phenomenon is attributed to a mechanism involving the discharge of hydroxyl ions on the clean metal surface to oxygen atoms which partly combine to form oxygen molecules and partly penetrate as such through the oxide film, leading to its further development and subsequently to the rapid depolarisation effect. The mechanism throws light on the process leading to the charging of an electrode surface in general, and explains satisfactorily the behaviour of antimony or arsenic electrodes involving the powdered metal in air.

OWING to the fact that it can be readily sublimed or obtained by the decomposition of suitable volatile products such as arsine, arsenic is one of the few metals that can be obtained free from oxide or absorbed oxygen. By carefully excluding oxygen during the deposition of the metal and from the test solutions, one can then obtain information regarding the mechanism of the electrode process of a metal with a clean surface. Such a condition was not satisfied with antimony electrodes prepared by electrolytic deposition and alternately subjected to the action of hydrogen and to high vacuum at ~350°, whereby only the labile oxygen film was removed but not the underlying layer of oxide. From the time of immersion, the potentials set up did not vary with time and the pH–potential curves were characterised by inflections corresponding to the titration of antimony trioxide first as an ortho-base and then as a meta-acid. In the present investigation, we report the behaviour of arsenic electrodes which were prepared by the two methods, *viz.*, sublimation of the metal in presence of hydrogen under conditions permitting only the deposition of the crystalline form, followed by degassing the metal under high vacuum, and decomposing arsine in the complete absence of oxygen.

EXPERIMENTAL.

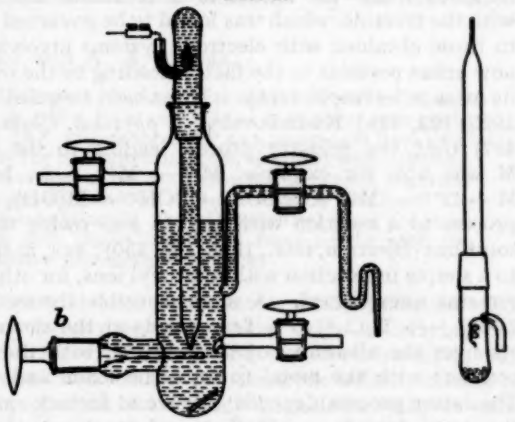
(A) *Preparation of the Electrodes by Sublimation.*—In following this procedure it was taken into consideration that hydrogen gas does not dissolve in the metal or lead under ordinary conditions to the formation of any compound (Fresenius and Babo, *Annalen*, 1844, **49**, 305; Reckleben and Scheiber, *Z. anorg. Chem.*, 1911, **70**, 255). The process involved the following steps.

(i) The powdered metal was heated for a sufficient time at 180—190° under a circulating atmosphere of pure hydrogen. The choice of this temperature range was based on the fact that the heat of formation of the octahedral oxide which is liable to be formed on the metal is 156,400 cals. (Bischowsky and Rossini, "Thermochemistry of Chemical Substances," New York, 1936, p. 40) and its reduction with hydrogen should be possible at 192° (St. John, *J. Physical Chem.*, 1929, **33**, 1438); further, that below this range, the oxide volatilises appreciably (Selmi, *Mem. Accad. Bologna*, 1878, **9**, 133) and at higher temperatures it may be transformed into the less volatile glassy form. (ii) The metal was sublimed in presence of hydrogen under conditions permitting only the deposition of the stable form. (iii) The deposited metal was degassed under a high vacuum.

The experiments were started by introducing some powdered arsenic from one of the sublimation columns into the electrode jacket, which was then sealed into a high-vacuum device surrounded with an electric heating-oven packed with asbestos. After thorough evacuation, as could be judged by a McLeod gauge, hydrogen [purified by the method of Hönigschmid *et al.* (*Z. anorg. Chem.*, 1927, **163**, 78)] was then gradually admitted and made to circulate with the aid of a mercury oscillating pump. Meanwhile, the temperature of the oven was raised to 180—190°, in which range the electrode jacket with the powdered metal was left for 30 minutes in the circulating hydrogen. The operation of evacuation and introducing new supplies of hydrogen was repeated at least 3 times before the device was allowed to attain the laboratory temperature in presence of hydrogen. The next steps involved drawing the narrow end of the electrode jacket (Fig. 1) to form a fine capillary, placing the heating oven about 1 cm. above the platinum spiral and maintaining it at 380°, and finally subliming the metal in presence of hydrogen with the aid of a micro-Bunsen burner so as to deposit it on the spiral in the form of bright metallic clusters.

After thorough evacuation, the electrode jacket was sealed off at the capillary constriction and carefully fitted into the electrode vessel holding the buffer solution, previously freed from any dissolved oxygen by bubbling in nitrogen purified according to Harcourt and Lupton (*Chem. News*, 1876, **33**, 90). When the tip of the capillary constriction was broken the buffer bathed the electrode and the measurements could then be made.

FIG. 1.



(B) *Preparation of Arsenic by Formation and Decomposition of Arsine.*—For the preparation of arsine a modified form of Robertson's apparatus (*Proc. Roy. Soc.*, 1928, **120**, 160) was used, and the arsine was prepared by the action of a solution of arsenious oxide in freshly boiled hydrochloric acid on pure magnesium turnings (Robinson *et al.*, *J.*, 1934, 730). This process as well as the process of decomposing the product could both be performed out of contact with air in a closed system that could be subjected to a high vacuum.

Electrodes prepared by method (A) were examined in Clark and Lubs's buffer solutions covering the pH range 1—10. Those prepared by method (B) were examined in the same buffers but only of the pH values 0·97, 3·00, 5·03, 6·99, and 8·95. All experimental details concerning the preparation of the buffers and the measurements were the same as described in previous papers.

RESULTS AND DISCUSSION.

In Fig. 2 are shown the log time–potential curves obtained with arsenic electrodes prepared by sublimation in presence of hydrogen. Essentially similar curves were obtained with electrodes

FIG. 2.

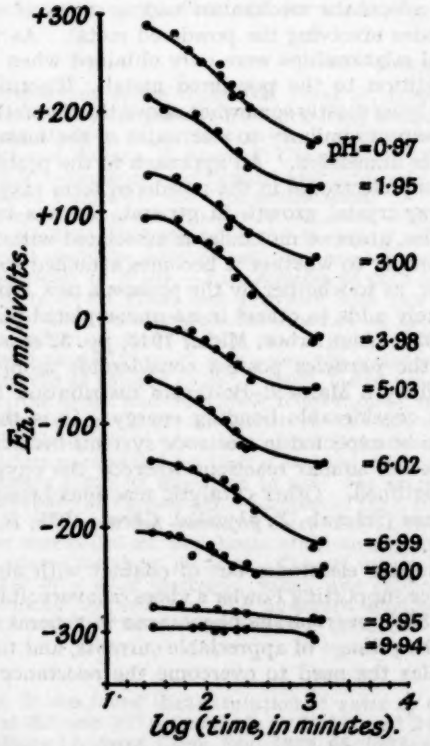
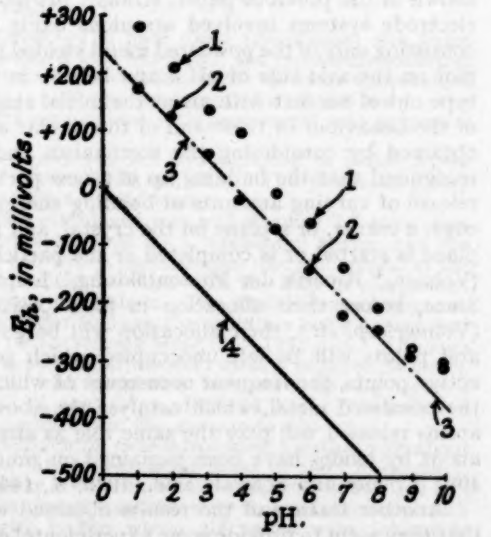


FIG. 3.



(1) *Initial potentials* (*~30 minutes after immersion*).
(2) *Final* ,, (*~20 hours* ,,).
(3) *Reversible* As–As_2O_3 *system.*
(4) ,, *hydrogen electrode system.*

prepared by decomposing arsine, thus indicating the reproducibility of the results for electrodes initially free from an oxide film or absorbed oxygen. As can be seen in all buffers except the most alkaline ones, the potentials set up on immersion decrease appreciably with time towards the thermodynamic values for the As–As_2O_3 system.

Fig. 3 representing the pH–potential plots based on the initial (30 minutes) and the final (48 hours) potentials reveals that both curves bear considerable analogy to the pH–potential plots obtained in air—the former to those manifested with massive arsenic electrodes in conjunction with the trioxide, which was found to be governed by an oxygen overvoltage effect, and the latter to those obtained with electrode systems involving the powdered metal. The question which now arises pertains to the factors leading to the overvoltage effect out of contact with air and to its more or less rapid decay. It has been assumed by earlier workers (Heyrovsky, *Proc. Roy. Soc.*, **1923**, **102**, 628; Kistiakovsky, *Z. physikal. Chem.*, **1910**, **70**, 206; Reichinstein, *ibid.*, **1920**, **95**, 457) that the primary process leading to the charging of an electrode surface of a metal M was not, for example, $M \longrightarrow M^{++} + 2e$, but was probably due to reactions such as $M + O^{--} = MO + 2e$ or $M + 2OH^- = M(OH)_2 + 2e$. Kinetically it is difficult to ascribe the process to a reaction with oxygen ions owing to the negligible quantity of these in aqueous solutions (Bjerrum, *ibid.*, **1923**, **106**, 230); nor, in the light of the present results, can it be ascribed to a simple interaction with hydroxyl ions, for otherwise the overvoltage effect initially observed remains unexplained. A more plausible theory for the charging process is that the reaction $2OH^- \longrightarrow H_2O + O + 2e$ proceeds at the clean metal surface and is the more stimulated the stronger the alkalinity of the solution, with the result that the oxygen atoms formed partly combine with the metal to form the oxide and partly aggregate to form oxygen molecules. The latter process depends on several factors, one of which is the mobility of these atoms on the electrode surface. If all atoms formed were capable of forming oxygen molecules, a persistent overvoltage effect would result owing to the impermeability of the film initially formed for the same reasons as those adduced in the case of the antimony electrodes. If, on the other hand, part of the oxygen atoms were capable of penetrating through the film—which is likely to be the case—the oxide will continuously develop on the electrode, disaggregating in its neighbourhood and depolarizing the overvoltage effect caused by the absorbed molecules. There is thus a marked difference between the effects caused by oxygen deposited from the gas phase and that formed by the discharge of hydroxyl ions, and this affects the mechanism leading to the attainment of the thermodynamic potentials with electrodes involving the powdered metal. As was shown in the previous paper, straight pH–potential relationships were only obtained when the electrode systems involved arsenious oxide in addition to the powdered metal. Electrodes consisting only of the powdered metal yielded points lying mostly somewhat above the theoretical plot on the acid side of pH 7 and behave in this respect similarly to electrodes of the massive type out of contact with air at the initial stage after immersion. An approach to the problem of the behaviour of these and of the similar antimony electrodes in the powdered form may be obtained by considering the mechanism underlying crystal growth in general. It has been recognised that the building up of a new particle (ion, atom or molecule) is associated with the release of varying amounts of bonding energy according to whether it becomes attached to an edge, a corner, or a plane on the crystal, and further, as to whether by the process a new lattice plane is started or is completed or the particle merely adds to others in an uncompleted plane (Volmer, "Kinetik der Phasenbildung," Leipzig, 1939; Ann Arbor, Mich., 1945, pp. 32 *et seq.*). Since, before their allocation in fixed positions, the particles possess considerable mobility (Volmer, *op. cit.*), their allocation will be governed by a Maxwell–Boltzman distribution law and points will be left unoccupied which possess considerable bonding energy. It is these active points, the frequent occurrence of which is to be expected in electrode systems involving the powdered metal, which catalyse the above or other similar reactions whereby the oxygen atoms released will play the same rôle as already outlined. Other catalytic reactions brought about by oxides have been explained on similar lines (Schwab, *Z. physikal. Chem.*, **1929**, *B*, **5**, 406; Cremer and Schwab, *ibid.*, **1929**, *A*, **144**, 243).

Another feature of the results obtained with arsenic electrodes out of contact with air is that they seem to provide some experimental evidence supporting Fowler's views on overvoltage. As he pointed out (*Trans. Faraday Soc.*, **1932**, **28**, 368), overvoltage phenomena in general are to be regarded rather as primary and essential for the passage of appreciable currents, and they are not in any way due to secondary effects such as the need to overcome the resistance of obstructive layers of gas as has been argued.

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283. *Studies on Some Metal Electrodes. Part VIII. The Bearing of the Properties of Arsenious Oxide on the Behaviour of the Arsenic Electrode.*

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From solubility measurements in buffers of different pH, arsenious oxide is found to behave as an ampholyte with its isoelectric point at *ca.* pH 4. On one side of that point, the oxide behaves as a monobasic acid with $K_a = 7{\cdot}4 \times 10^{-9}$, and on the other as a mono-acid base with $K_b = 1{\cdot}8 \times 10^{-14}$. In the light of these results the pH–potential plots obtained with different arsenic electrodes, and extending over different ranges of pH according to the type of electrode used, are satisfactorily explained. Owing to the localisation of the isoelectric point and the simpler mode of dissociation in solution of arsenic trioxide, the pH–potential plots obtained with arsenic electrodes of the massive type give slopes coinciding more nearly with the theoretical than do those obtained with massive antimony electrodes.

In the well-known relation connecting the potential of a metal–metal oxide electrode with pH no account is taken of the amphoteric or other properties of the oxide underlying the functioning of the electrode. Deviations from a linear course cannot, therefore, be explained, and it is deemed necessary to plot a calibration relation for any one electrode before utilising it for the measurement of pH. By studying the properties of antimony trioxide in bulk, we were able to interpret the pH–potential curves obtained with the antimony electrode after removal of the oxygen film from its surface, and it was suggested that they represent titration curves of the ortho-base below, and of the meta-acid above its isoelectric point (*J.*, 1948, 759). In this paper, the properties of arsenious oxide in solution are studied by a somewhat different procedure, and it is shown that owing to the position of its isoelectric point and its simpler mode of dissociation as an acid or base, the pH–potential curves obtained with electrodes of different types are satisfactorily explained, and also that, in its massive form, the electrode is better than the antimony electrode for measuring pH.

Experimental.

Preparation of the Octahedral Form of Arsenious Oxide.—The pure oxide (Kahlbaum) was twice recrystallised from pure hydrochloric acid, thoroughly washed with hot water, and repeatedly sublimed in pure nitrogen at *ca.* 195° so as to obtain the octahedral modification stable at room temperature (Smits and Beljaar, *Z. physikal. Chem.*, 1933, **167**, 273). Although the temperature is too low for the oxide to decompose into element and pentoxide, a slight grey residue with pronounced acid properties remained even after the fifth sublimation.

Preparation of the Vitreous Modification.—The above pure product was sublimed in sealed Pyrex flasks at 375—400° (Randall and Doody, *J. Physical Chem.*, 1939, **43**, 613). The protected glassy material could be kept as such for several months without devitrification.

Solubility in Water.—Pure samples of each form were introduced into well-steamed 2-l. saturation vessels of Pyrex glass, each provided with two mercury seals—one for a mechanical stirrer, and the other for an inverted syphon furnished at the ascending end with a sintered-glass disc and ground at the other end so as to fit tightly into a pyknometer. This could be filled with the help of compressed nitrogen passing through a two-way tap sealed at the neck of the flask. The solubility measurements, carried out at 25° and at 35° ± 0·05°, lasted usually for about 50 days, the equilibria being approached both from higher and from lower temperatures, and the rate of stirring being 150—175 r.p.m. Although arsenious oxide sols are not known to exist, the complete settling of the solid usually required 24 hours.

Dissolved As^{+++} was determined potentiometrically with potassium bromate following Győry's procedure as modified by Zintl *et al.* (*Ber.*, 1923, **56**, 472; *Z. anal. Chem.*, 1928, **74**, 330). The inflexion indicating complete oxidation to As^{5+} was sharp and amounted in the average to 400 mv.

Solubility at Various pH.—Samples of the pure octahedral form were introduced, together with about 60 c.c. of a standard buffer of Clark and Lubs's series, into well-steamed flasks of 100 c.c. capacity. These were sealed off, fixed horizontally on a vertical shaft in a water thermostat adjusted at 25° ± 0·05°, and rotated for about 60 days. The pH values of the saturated solutions were then redetermined with the aid of a glass electrode, which was calibrated with buffers whose pH values were accurately determined by means of the hydrogen electrode. The arsenic content of each solution was also determined by the above-mentioned method.

Results.

(i) It was found that saturation of water by the octahedral form is complete after about one month and at 25° and 35° corresponds to 2·0681 and 2·6620 g. per 100 g. of solution, respectively; Anderson and Story (*J. Amer. Chem. Soc.*, 1923, **45**, 1102) give 2·0506 and 2·5636. The solubilities of the vitreous form after the same time are 3·8237 and 3·2975 g. per 100 g. of solution at 25° and 35°, respectively; but these are not equilibrium solubilities since the values tend to decrease with time more quickly at 35° than at 25°, apparently owing to the transformation of the vitreous form *via* the monoclinic into the octahedral one. Similar observations were made by Bussy (*Compt. rend.*, 1847, **24**, 774) and by Winkler (*J. pr. Chem.*, 1847, **24**, 139).

(ii) By plotting the solubility S in the buffers against their original pH values on the one hand and against their pH values at saturation on the other, curves *a* and *b* respectively (Fig. 1) are obtained, showing that S passes through a minimum at about pH 4, which corresponds therefore to the isoelectric point of the trioxide. In Fig. 2 the pH values at saturation are plotted against the original pH, and

FIG. 1.

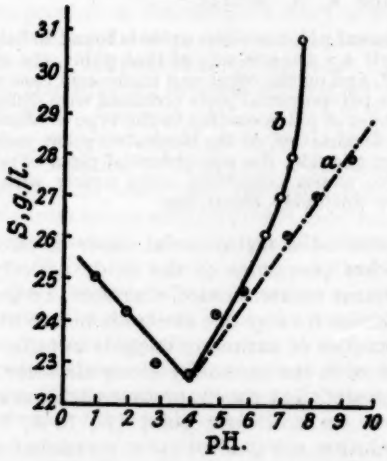
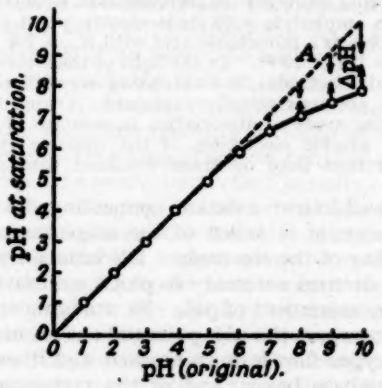
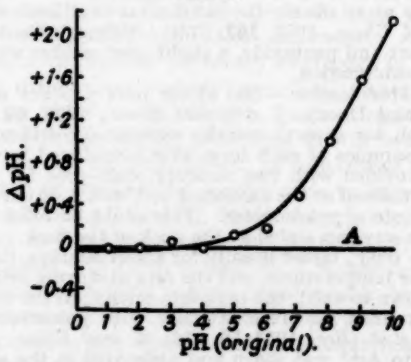


FIG. 2.



from this and from the curved line in Fig. 1, it can be seen that the introduction of the oxide affects the pH values of the buffers to an extent increasing with rise of pH. Below pH 7 the effect becomes progressively less marked and all points fall practically on the theoretical line *A* of unit slope. According to Michaelis (*Biochem. Z.*, 1912, **47**, 251), the point of zero Δ pH, which corresponds to the isoelectric point, may be determined by plotting the Δ pH values against the original pH's as shown in Fig. 3. The point of interception of the resulting curve with the straight line *A* of zero slope, although lying in the neighbourhood of pH 4, is not as clearly defined as by the S–pH plots.

FIG. 3.



In order to evaluate the magnitudes of the acid and basic dissociation constants, use was made of the following relations (Krebs and Speakman, *J.*, 1945, 593):

$$\log (S/S^\circ - 1) = \mathrm{pH} - \mathrm{p}K_a' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$\log (S/S^\circ - 1) = \mathrm{p}K_w - \mathrm{p}K_b' - \mathrm{pH} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

S being the total solubility and S° that in strongly acid solutions; S° may be evaluated by plotting S against $1/[H^+]$ and extrapolating to $1/[H^+] = 0$. The values of S at pH 4·49 and 5·80 lead to $S^\circ = 20{\cdot}40$ g./l. The $\log (S/S^\circ - 1)$ values are then calculated and found to be as follows:

pH at saturation	1·00	1·99	2·95	3·99	4·88
$1 + \log (S/S^\circ - 1)$	0·342	0·255	0·079	0·041	0·255
pH at saturation	5·80	6·50	7·00	7·38	7·83
$1 + \log (S/S^\circ - 1)$	0·322	0·413	0·505	0·556	0·708

By plotting the $1 + \log (S/S^\circ - 1)$ values against pH at saturation, a curve almost identical with the S–pH plot (curve *b* in Fig. 1) is obtained. By applying equation (1) and using as the most alkaline

buffers those with the pH values 7·83 and 7·38, K_a' is found to be $7{\cdot}4 \times 10^{-9}$ and $1{\cdot}5 \times 10^{-8}$, respectively. Equation (2) leads to K_b' values ranging from 22 to $1{\cdot}8 \times 10^{-14}$. The values of K_a' and K_b' are comparable with those obtained by other methods by other authors, which range from 10^{-10} to 10^{-11} for K_a' (Zwadisky, *Ber.*, 1903, **36**, 1435; Wood, *J.*, 1908, **93**, 415) and from 10^{-14} to 10^{-15} for K_b' (Wood, *loc. cit.*; Washburn *et al.*, *J. Amer. Chem. Soc.*, 1913, **35**, 681).

Discussion.

Because arsenious oxide gives an acid solution in water, the reaction $As_2O_3 + H_2O = 2AsO_2' + 2H^+$ has been assumed to occur. Such a representation is, however, too limited, and should be replaced by a set of dynamic equilibria such as:

$$\begin{array}{lll} & 2AsO_2^- + 2H^+ & \\ & \uparrow\downarrow & \\ & 2HAsO_2 + 2H_2O \quad . \ . \ . \ . \quad (1) & \\ As_2O_3 + 3H_2O \rightleftharpoons 2As^{+++} + 6OH^- & & \\ & 2AsO(OH) + 2H_2O \quad . \ . \ . \ . \quad (2) & \\ & \uparrow\downarrow & \\ & 2AsO^+ + 2OH^- & \end{array}$$

which allows for the existence of As^{+++} ions and thus satisfies the simple relation connecting the potential of a metal–metal oxide electrode and pH. Owing to their amphoteric and other properties, the As^{+++} ions are incapable of existing in appreciable quantity in water. This accounts for the ability of the electrode to function as an indicator electrode for pH in spite of the high solubility of the underlying oxide. The assumption tacitly accepted, that for a metal to function as a metal–metal oxide electrode its oxide should possess very low solubility, appears therefore to be unnecessary.

At the isoelectric zone both reactions indicated by (1) and (2) have equal opportunities to occur and outside that zone, either one may prevail. Considering now reaction (1), it may be noted that $HAsO_2$ will remain practically undissociated as long as the prevailing pH is lower than its pK_a' value, and any decrease in pH will bring about a corresponding increase in activity of As^{+++} ions. As the pH increases, the acid progressively dissociates until a pH value of the same magnitude as the pK_a' value of the acid is approached, whereupon the acid loses its identity owing to the incidence of the acid–base reaction. Higher pH values are then levelled down owing to the same effect. The same applies *mutatis mutandis* to the reaction represented by (2) in which case the conjugate acid, C_a, of the base AsO(OH) should be considered since all statements are made in terms of pH and not pOH. If the well-known relation $K_{C_a}K_b' = K_w$ is applied and K_w taken as 10^{-14}, K_{C_a} will be approximately unity, and pK_{C_a} zero, and hence any deviations resulting from a base–acid reaction below the isoelectric zone will be negligible above pH = 0.

In the light of these properties of solutions of arsenious oxide, we can now interpret the pH–potential plots given by the different types of arsenic electrode. For instance, polarised electrodes consisting of the freshly prepared massive metal show a linear course over the pH range 3—10 owing to the inability of the oxide on the surface of the metal to level down the buffer above pH 7 or to depolarise the electrode in strongly acid solutions. When the electrodes are used in conjunction with the trioxide, the linear course extends only over the pH range 4—7, the flattening of the curves above that pH being greater with the more soluble vitreous than with the octahedral form of the oxide. Aged electrodes show intermediate behaviour and respond rightly to variations in pH between pH 3 and 8.

Unpolarised electrodes, on the other hand, *i.e.*, electrodes involving the powdered metal, show a linear course between pH 1 and 7 when the trioxide is involved in the electrode systems and this is in harmony with the properties of both electrode and oxide. Otherwise, the relation is not a strictly linear one; the points lying mostly either above or below the theoretical plot on the acid or the alkaline side of pH 7, respectively. It is probable that the mechanism of oxidation of the powdered metal leads to a slight polarisation effect which more or less persists in the absence of appreciable portions of the oxide to saturate the buffers. Out of contact with air the pH–potential plots as based on the final potential values constitute straight lines extending through the approximate pH range 1—7.

A remarkable feature of the pH–potential plots obtained with arsenic electrodes of all types

is that, although they extend over different pH ranges according to the type of electrode and for the reasons outlined above, they all manifest a slope, the magnitude of which, in contrast to that of the antimony electrode, coincides closely with the theoretical one. This is apparently connected with the mode of dissociation of arsenious hydroxide simply as a meta-base or acid on both sides of its isoelectric point. Antimony hydroxide was found to behave as an ortho-base below and as a meta-acid above its iso-electric point at *ca.* pH 9 (*loc. cit.*). Although in air the properties of the oxide formed on massive antimony electrodes were masked by the oxygen overvoltage effect, yet owing to its dissociation in steps and to the position of its isoelectric point, the pH–potential plots obtained with such electrodes were found to possess slopes deviating from the theoretical one.

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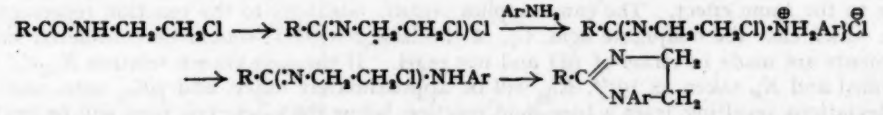
284. *Synthesis of* 1-*Aryl*-4 : 5-*dihydroglyoxalines.*

By M. W. PARTRIDGE and H. A. TURNER.

An *N*-2-chloroethylcarboxyamide, when converted into the corresponding imido-chloride in the presence of an arylamine, affords an *N'*-substituted *N*-2-chloroethylamidinium chloride, which is cyclized to a 1-aryl-4 : 5-dihydroglyoxaline on treatment with alkali.

2-SUBSTITUTED 1-alkyl-4 : 5-dihydroglyoxalines are known to exhibit a wide range of biological activity (see, *e.g.*, Kyrides, Zienty, Steahly, and Morrill, *J. Org. Chem.*, 1947, **12**, 577), whereas little appears to be known of the activities of 2-substituted 1-aryl-4 : 5-dihydroglyoxalines. Clayton (*Ber.*, 1895, **28**, 1665) has described the preparation of a few 2 : 5-disubstituted 1-aryl-4 : 5-dihydroglyoxalines from *N*-allylcarboxyamides and amine hydrochlorides. Possible extensions of the more elegant methods for the production of 2-substituted 4 : 5-dihydroglyoxalines (Oxley and Short, *J.*, 1947, 497; Chitwood and Reid, *J. Amer. Chem. Soc.*, 1935, **57**, 2424; Scholtz, *Ind. Eng. Chem.*, 1945, **37**, 120; Kyrides *et al.*, *loc. cit.*) appeared inapplicable to 2-substituted 1-aryl-4 : 5-dihydroglyoxalines because of the inaccessibility of the necessary intermediates.

We find that the method of preparing an *NN'*-disubstituted amidine from an *N*-substituted carboxyamide, *via* an imido-chloride can be adapted to the production of 2-substituted 1-*aryl*-4 : 5-*dihydroglyoxalines* in good yield from *N*-2-chloroethylcarboxyamides:



N-2-Chloroethylcarboxyamides are easily prepared by a rearrangement of imino-2-chloroethyl ethers, which are readily accessible (Gabriel and Neumann, *Ber.*, 1892, **25**, 2383; Wislicenus and Körber, *Ber.*, 1902, **35**, 164) and thereby one avoids the unsatisfactory acylation of the vesicant, 2-chloroethylamine. *N*-2-Chloroethylbenzamide, treated with phosphorus pentachloride, afforded N-2-*chloroethylbenzimidochloride* in 70% yield. Imido-chlorides, $R'\cdot CH_2\cdot C(:NR'')Cl$, are very unstable and readily change into chlorovinylamidinium chlorides (Heymons, *Ber.*, 1932, **65**, 320). By conducting the conversion of an *N*-2-chloroethylcarboxyamide,

$$R'\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CH_2Cl,$$

into the imido-chloride in the presence of an arylamine, a change of this type does not occur, and the expected *NN'*-disubstituted amidinium chloride is obtained. In this way, N-2-*chloroethyl*-N'-*phenyl*- and N'-p-*tolyl*-*phenylacetamidinium chloride* were prepared in 87% and 97% yields respectively. The corresponding free *NN'*-disubstituted amidines could not be isolated because of the extreme facility with which cyclization occurred. Indeed, attempts to convert these amidinium chlorides into their picrates resulted in the formation of the corresponding *dihydroglyoxaline picrates*. *N*-2-Chloroethylbenzimidochloride and aniline afforded a product which could not be crystallised but similarly yielded 1 : 2-*diphenyl*-4 : 5-*dihydroglyoxaline picrate* (91%). Treatment of *N*-2-chloroethyl-*N'*-phenyl- and -*N'*-*p*-tolyl-phenylacetamidinium chloride with alkali yielded respectively 1-phenyl-2-benzyl-4 : 5-dihydroglyoxaline (95%), characterised as its picrate and *Reineckate*, and 1-p-*tolyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline* (97%), characterised as its picrate. The complete series of changes is readily effected; the *N*-2-chloro-

ethylcarboxyamide is converted into the corresponding imido-chloride in the presence of an arylamine, and the 1-aryl-4 : 5-dihydroglyoxaline is obtained from the resulting amidinium chloride by treatment with alkali. The scope of the process is illustrated by the examples described in the experimental section.

Because the rearrangement of an imino 2-chloroethyl ether to a 2-chloroethylcarboxyamide involves an oxazoline as an intermediate (Wislicenus and Körber, *loc. cit.*), and in order to avoid, if possible, the use of aqueous alkali hydroxides in this reaction, experiments were carried out on the use of ammonia under anhydrous conditions. *Phenylacetimino 2-chloroethyl ether hydrochloride* with ethereal ammonia yielded *N*-2-chloroethylphenylacetamide (52%) and 2-benzyloxazoline (41%); with ethanolic ammonia, phenylacetamidine (78%) was obtained. Benzimino 2-chloroethyl ether hydrochloride with ethanolic ammonia afforded 2-phenyloxazoline (72%) and benzamidine (10%).

Experimental.

Phenylacetimino 2-Chloroethyl Ether Hydrochloride.—A mixture of ethylene chlorohydrin (28 g.), dried by refluxing with benzene under a phase separator and fractionation, with benzyl cyanide (35 g., 0·85 mol.) was saturated at 0° with anhydrous hydrogen chloride and kept at 0° overnight. The powdered *hydrochloride* (69 g.; 98%) was washed with anhydrous ether; m. p. 160° (decomp.) (Found : N, 6·05, 6·1. $C_{10}H_{13}ONCl_2$ requires N, 6·0%). In anhydrous ether, the yield decreased to 66 g. (94%).

N-2-*Chloroethylphenylacetamide.*—(*a*) The base liberated at 0° by potassium hydroxide from the foregoing hydrochloride (46·8 g.) was collected in ether, dried, and, after recovery from the ether, heated at 130° for 1 hour. The crude product (30 g., m. p. 66°), obtained by extraction with benzene, crystallised from light petroleum (b. p. 60—80°); m. p. 80° (29·5 g.; 75%) (Found : N, 7·1; Cl, 17·8. Calc. for $C_{10}H_{12}ONCl$: N, 7·1; Cl, 18·0%). When isomerisation was effected at 100° for 30 minutes, the yield was 7·55 g. (19%).

(*b*) The product obtained on interaction of phenylacetyl chloride (11·6 g.), 2-chloroethylamine hydrochloride (15·5 g.; 1·02 mols.) (Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914), and 5N-sodium hydroxide (42 c.c.) under Schotten–Baumann conditions was crystallised from light petroleum (b. p. 60—80°); yield 5·5 g. (28%); m. p. and mixed m. p. 80°. Phillips and Baltzly (*J. Amer. Chem. Soc.*, 1947, **69**, 200) describe a compound, m. p. 82—83°, which they thought to be impure *N*-2-chloroethylphenylacetamide.

N-2-*Chloroethylbenzamide.*—(*a*) The base, obtained from benzimino 2-chloroethyl ether hydrochloride (Gabriel and Neumann, *loc. cit.*) as described for *N*-2-chloroethylphenylacetamide, was heated at 100° for 30 minutes. The crude *N*-2-chloroethylbenzamide was crystallised from benzene–light petroleum (b. p. 80—100°); yield 26 g. (86%); m. p. 105°. Gabriel and Neumann (*loc. cit.*) record m. p. 102—103° for this substance.

(*b*) The product which separated when benzoyl chloride (7 g.) was gradually added, with vigorous shaking, to a solution of 2-chloroethylamine hydrochloride (5·8 g.; 1 mol.) in 5N-sodium hydroxide (20 c.c.; 1 mol.) was crystallised from benzene–light petroleum; yield 8 g. (87%); m. p. 105°, undepressed on admixture with material prepared from benzimino 2-chloroethyl ether hydrochloride.

N-2-*Chloroethylbenzimidochloride.*—A mixture of 2-chloroethylbenzamide (9·2 g.) and phosphorus pentachloride (11·5 g.; 1·1 mols.), heated together at 110° for 3 hours and fractionated in a vacuum, afforded N-2-*chloroethylbenzimidochloride* (7·1 g.; 70%), b. p. 120—122°/1 mm. (Found : N, 6·9. $C_9H_9NCl_2$ requires N, 6·9%).

N′-*Phenyl*-N-2-*chloroethylphenylacetamidinium Chloride.*—Finely powdered phosphorus pentachloride (5·75 g.) was dissolved in dry benzene (30 c.c.), *N*-2-chloroethylphenylacetamide (4·9 g.; 0·9 mol.) in dry benzene (20 c.c.) was added, the mixture was heated under reflux for 10 minutes, aniline (2·35 g.; 0·91 mol.) was added gradually, and the mixture was heated under reflux for 3 hours. The residue, left on evaporation under reduced pressure, afforded N′-*phenyl*-N-2-*chloroethylphenylacetamidinium chloride* on crystallisation from aqueous alcohol; m. p. 193—194°; yield 6·7 g.; 87% (Found : C, 62·0; H, 5·9; Cl′, 11·3. $C_{16}H_{17}N_2Cl,HCl$ requires C, 62·1; H, 5·9; Cl′, 11·5%).

N′-p-*Tolyl*-N-2-*chloroethylphenylacetamidinium Chloride.*—The method used was as described for the preceding preparation, *p*-toluidine (2·7 g.; 0·91 mol.) being used instead of aniline. N′-p-*Tolyl*-N-2-*chloroethylphenylacetamidinium chloride* crystallised from water; m. p. 196—197°; yield 7·8 g. (97%) (Found : N, 8·75. $C_{17}H_{20}N_2Cl_2$ requires N, 8·7%).

1-*Phenyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline.*—(*a*) *N′*-Phenyl-*N*-2-chloroethylphenylacetamidinium chloride (6·2 g.) was dissolved in warm water, and the solution made alkaline to Titan-yellow with 5N-sodium hydroxide and extracted with chloroform. The basic gum (4·7 g.), obtained on evaporation, afforded 1-*phenyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline picrate* on neutralisation to brilliant-yellow with alcoholic picric acid; needles from aqueous alcohol, m. p. 188°; yield 8·8 g. (95%) (Found : C, 57·0; H, 4·1; N, 15·15. $C_{22}H_{19}O_6N_5$ requires C, 56·8; H, 4·1; N, 15·05%).

(*b*) A warm aqueous solution of *N′*-phenyl-*N*-2-chloroethylphenylacetamidinium chloride (3·1 g.), with excess of neutral saturated aqueous sodium picrate, afforded the same compound (4·2 g.; 90%), m. p. and mixed m. p. after recrystallisation, 188°. The *Reinechate* crystallised from aqueous acetone; m. p. 158—159° (decomp.) (Found : SCN, 41·8. $C_{16}H_{16}N_2,H[Cr(SCN)_4(NH_3)_2]$ requires SCN, 41·8%).

1-p-*Tolyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline.*—(*a*) The method described for the phenyl analogue was used; 12 g. of *N′*-*p*-tolyl-*N*-2-chloroethylphenylacetamidinium chloride yielded 9·1 g. of basic gum which, with picric acid, afforded 1-p-*tolyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline picrate* (17·3 g.; 97%); needles from aqueous ethanol, m. p. 170° (Found : N, 14·4. $C_{23}H_{21}O_7N_5$ requires N, 14·6%).

(*b*) The same compound was obtained by interaction of the substituted amidinium chloride and neutral sodium picrate solution; m. p. and mixed m. p. 170°.

1 : 2-*Diphenyl*-4 : 5-*dihydroglyoxaline.*—(*a*) *N*-2-Chloroethylbenzimidochloride (3·4 g.) and aniline

(1·55 g.; 1 mol.) were mixed in dry benzene (10 c.c.) and heated under reflux for 90 minutes. The gum which separated could not be obtained crystalline; an aqueous solution, after being decolorised with charcoal and treated with saturated aqueous picric acid, afforded 1 : 2-*diphenyl*-4 : 5-*dihydroglyoxaline picrate* (6·8 g.; 91%); prisms from ethanol, m. p. 174—175° (Found: N, 15·6. $C_{21}H_{17}O_7N_5$ requires N, 15·6%).

(*b*) Phosphorus pentachloride (11·5 g.) was dissolved in dry benzene (50 c.c.), *N*-2-chloroethylbenzamide (9·2 g.; 0·9 mol.) was added and dissolved, and then aniline (4·65 g.; 0·9 mol.), dissolved in benzene (20 c.c.), was added slowly. The mixture was heated under reflux, protected by a calcium chloride tube, for 3 hours, and the solvent and phosphorus oxychloride were evaporated off in a vacuum. A solution of the residue in hot water (250 c.c.) was treated with charcoal; the *base*, liberated by ammonia, collected in chloroform, and recovered by evaporation, crystallised slowly from benzene–light petroleum (b. p. 80—100°); yield 10·2 g. (92%), m. p. 74—75° (Found: N, 12·5. $C_{15}H_{14}N_2$ requires N, 12·6%). The *toluene*-p-*sulphonate* crystallised when an equivalent of toluene-*p*-sulphonic acid was added to a solution of the base in *iso*propanol; m. p. 205—207° (Found: N, 7·0. $C_{22}H_{22}O_3N_2S$ requires N, 7·1%). The picrate was obtained by interaction of a solution of the base in an equivalent of N-hydrochloric acid and sodium picrate solution; m. p. and mixed m. p. with material prepared as described above, 174—175°.

2-*Phenyl*-1-p-*tolyl*-4 : 5-*dihydroglyoxaline*.—The method (*b*) described for the 1 : 2-diphenyl analogue was employed, *p*-toluidine (5·4 g.; 0·91 mol.) being used instead of aniline; the base (11·7 g.) was converted into the *toluene*-p-*sulphonate*; colourless prisms from *iso*propanol, m. p. 165°; yield 18·8 g. (91%) (Found: N, 7·0. $C_{23}H_{24}O_3N_2S$ requires N, 6·85%). The *picrate* crystallised from aqueous ethanol; m. p. 162—163° (Found: N, 15·2. $C_{22}H_{19}O_7N_5$ requires N, 15·05%).

2-*Phenyl*-1-p-*chlorophenyl*-4 : 5-*dihydroglyoxaline*.—*p*-Chloroaniline (6·4 g.; 0·9 mol.) was used in place of aniline in the same method (*b*); the base (12·1 g.) afforded the *toluene*-p-*sulphonate*, which crystallised from *iso*propanol; m. p. 163—164°; yield 19·2 g. (90%) (Found: N, 6·5. $C_{23}H_{21}O_3N_2ClS$ requires N, 6·5%). The *picrate*, yellow needles from aqueous ethanol, had m. p. 190° (Found: N, 14·5. $C_{21}H_{16}O_7N_5Cl$ requires N, 14·4%).

2-*Phenyl*-1-p-*nitrophenyl*-4 : 5-*dihydroglyoxaline*.—The volume of benzene employed in a procedure analogous to that (*b*) described for the 1 : 2-diphenyl analogue was increased to 200 c.c. owing to the lower solubility of *p*-nitroaniline (6·9 g.; 0·97 mol.). The *dihydroglyoxaline* crystallised from *iso*propanol in yellow leaflets, m. p. 177·5°; yield, 8·9 g. (67%) (Found: C, 67·2; H, 5·1; N, 16·1. $C_{15}H_{13}O_2N_3$ requires C, 67·4; H, 4·9; N, 15·7%). The *picrate* crystallised from chloroform, m. p. 173—174° (Found: N, 17·2. $C_{21}H_{15}O_9N_8$ requires N, 16·95%).

2-*Phenyl*-1-2′-*naphthyl*-4 : 5-*dihydroglyoxaline*.—2-Naphthylamine (7·15 g.; 0·9 mol.) was employed in the usual method. The *base* (12·3 g.; 90%) crystallised from benzene, m. p. 131° (Found: C, 83·2; H, 6·0; N, 10·1. $C_{19}H_{16}N_2$ requires C, 83·8; H, 5·9; N, 10·3%). The *toluene*-p-*sulphonate* crystallised from *iso*propanol; m. p. 106° (Found: N, 6·0. $C_{26}H_{24}O_3N_2S$ requires N, 6·3%). The *picrate* was obtained as needles from aqueous ethanol; m. p. 230° (Found: N, 14·1. $C_{25}H_{19}O_7N_5$ requires N, 14·0%).

Ammonolysis of Phenylacetimino 2-Chloroethyl Ether.—(*a*) A suspension of finely powdered phenylacetimino 2-chloroethyl ether hydrochloride (18 g.) in anhydrous ether (250 c.c.) was treated with a stream of dry ammonia for 48 hours. After removal of ammonium chloride, the ether was evaporated; towards the end of the evaporation, an exothermic reaction occurred and the temperature of the residue rose from 40° to 120°. The product was separated into basic (5·3 g.) and neutral (8·1 g.) fractions by extraction with aqueous lactic acid. The neutral fraction crystallised from light petroleum (b. p. 80—100°) (7·9 g.; 52%), m. p. 79—80°, not depressed on admixture with *N*-2-chloroethylphenylacetamide (Found: N, 7·2. Calc. for $C_{10}H_{12}ONCl$: N, 7·1%). The solution of the lactate of the basic fraction, when treated with excess of sodium picrate, afforded 2-benzyloxazoline picrate (12·1 g.; 41%); m. p. 144°. Elfeldt (*Ber.*, 1891, **24**, 3218) records m. p. 130—131° for this compound (Found: N, 14·2. Calc. for $C_{16}H_{14}O_8N_4$: N, 14·35%).

(*b*) A solution of phenylacetimino 2-chloroethyl ether hydrochloride (4·7 g.) in anhydrous ethanol (50 c.c.) containing dry ammonia (4·5 g.) was kept for 6 hours. The solvent was removed under reduced pressure, the residue basified with 5N-sodium hydroxide (5 c.c.), and the base collected in chloroform. The dry chloroform solution, divided into equal parts, afforded (i) with alcoholic picric acid, phenylacetamidinium picrate, m. p. 227—228°, not depressed on admixture with an authentic specimen (2·85 g.; 78%) (Found: N, 19·4. Calc. for $C_{14}H_{13}O_7N_5$: N, 19·3%), and (ii) with benzenesulphonic acid, phenylacetamidinium benzenesulphonate, m. p. and mixed m. p. 185—186° (Oxley and Short, *J.*, 1946, 147).

Ammonolysis of Benzimino 2-Chloroethyl Ether.—A solution of benzimino 2-chloroethyl ether hydrochloride (4·4 g.) in anhydrous ethanol (50 c.c.) containing dry ammonia (4·5 g.) was kept for 6 hours. Removal of the solvent and extraction with ether followed by fractionation afforded 2-phenyloxazoline, b. p. 245° (decomp.) (2·1 g.; 72%); picrate, m. p. 180—180·5°, not depressed on admixture with the picrate prepared according to Gabriel and Heymann (*Ber.*, 1890, **23**, 2493) (Found: N, 15·0. Calc. for $C_{15}H_{12}O_8N_4$: N, 14·9%). The ether-insoluble residue, after being basified with 5N-sodium hydroxide and collected in chloroform, yielded, with alcoholic picric acid, benzamidinium picrate, m. p. 238—238·5°, not depressed on admixture with authentic benzamidinium picrate (0·7 g.; 10%).

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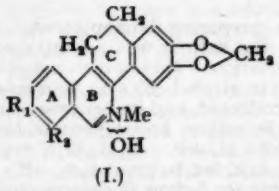
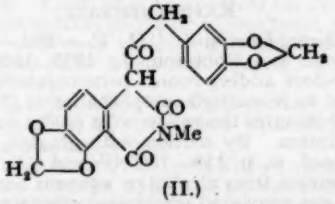
285. *Experiments on the Synthesis of the* Chelidonium *Alkaloids.*

By H. S. Forrest, R. D. Haworth, A. R. Pinder, and T. S. Stevens.

Several synthetic routes to the benzphenanthridine system have been explored, using initial materials derived from (*a*) homophthalic acid, (*b*) benzyl-1-naphthylamine. A new synthesis is described of the methylenedioxymethylphenanthridone which Kondo obtained in the degradation of lycorine. By the action of sodium, ethyl homophthalate affords, probably, a naphthalene derivative.

Degradative studies by Gadamer and Späth (*Ber.*, 1931, **64**, 370, 1123, 2034) and their co-workers have shown that the *Chelidonium* alkaloids, *e.g.*, chelerythrine (I, $R_1 = R_2 = MeO$) and sanguinarine (I, $R_1R_2 = CH_2O_2$), are derivatives of 1 : 2-benzphenanthridine. Noller, Denyes, Gates, and Wasley (*J. Amer. Chem. Soc.*, 1937, **59**, 2079) report preliminary synthetic experiments, including some, based on Pschorr's phenanthrene synthesis, which are complementary to work described below. The synthesis of the tetracyclic system by Richardson, Robinson, and Seijo (*J.*, 1937, 835) is not readily adaptable to the production of a molecule vicinally substituted in ring A. In view of the availability of suitably oriented dimethoxy- and methylenedioxy-homophthalic acids, Haworth (*ibid.*, p. 1312) attempted, unsuccessfully, to effect ring-closure in the homophthalimide derivative (II).


(I.)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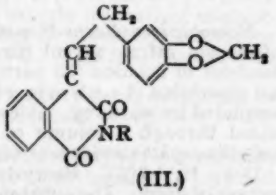
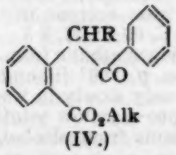

(III.)

Homophthalimide and its *N*-methyl derivative have now been condensed with homopiperonal; the *products*, presumably (III), were unstable and numerous attempts at ring-closure failed.

The potentially serviceable ester (IV, $R = CO_2Et$) should be obtainable by condensation of ethyl homophthalate with ethyl benzoate, but the sole definable *product*, $C_{20}H_{14}O_5$, was also formed by treating ethyl homophthalate alone with sodium. This substance was a monohydric phenol, yielding a *methyl ether* and a p-*nitrobenzoate*; it behaved as a lactone and is believed to be one of the two isomers derivable from the acid (V).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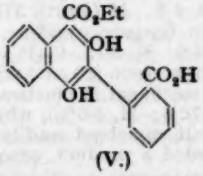
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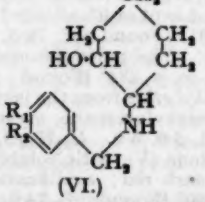
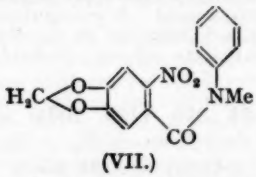

(VI.)

Methyl o-*phenacylbenzoate*, $Ph{\cdot}CO{\cdot}CH_2{\cdot}C_6H_4{\cdot}CO_2Me$, obtained from homophthalic anhydride through the Friedel–Crafts reaction, was treated with ethyl bromoacetate and sodium ethoxide in order to prepare (IV, $R = CH_2{\cdot}CO_2Et$), which contains the complete carbon skeleton of benzphenanthridine. This could not be effected, and similar attempts to condense o-*carbomethoxybenzyl cyanide* with ethyl bromoacetate and with ω-bromoacetophenone failed.

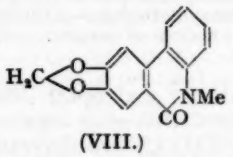
In another method of approach, 2 : 3-methylenedioxy- or 2 : 3-dimethoxy-benzaldehyde could contribute ring A, and ring B be closed by establishing the bond between rings A and C. This ring-closure was first attempted in the *compounds* (VI, $R_1R_2 = 2MeO$ or CH_2O_2), readily obtained from the appropriate primary amines and *cyclo*hexene oxide, and in their *N*-methyl derivatives. In no case could cyclo-dehydration be effected [compare Staub's generalisations as to the scope of the Pomeranz–Fritzsch synthesis of simple *iso*quinolines (*Helv. Chim. Acta*, 1922, **5**, 888)].

Pictet and Gonset (*Arch. Sci. phys. nat.*, 1897, **3**, 37) applied the Pschorr phenanthrene synthesis to the preparation of *N*-methylphenanthridone from *o*-nitrobenzoylmethylaniline. Similarly, by reduction and diazotisation, 2′-*nitro*-4′ : 5′-*methylenedioxybenzomethylanilide* (VII) gave in fairly good yield 6 : 7-methylenedioxy-10-methylphenanthridone (VIII), which Kondo and Uyeo (*Ber.*, 1935, **68**, 1756) encountered in the degradation of lycorine and synthesised by a less effective method. 2′-*Nitro*-4′ : 5′-*methylenedioxybenzomethyl*-1-*naphthalide* was prepared

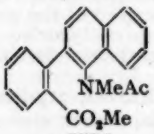
and reduced, but numerous attempts to effect ring-closure to a benzphenanthridone failed. The acid-sensitive *amine* obtained by reducing *2'-nitro-4' : 5'-methylenedioxybenzyl*-N-*methylaniline* (VII; CH_2 for CO) gave no identifiable product on diazotisation and warming. *Nitromethylenedioxybenzylmethylnaphthylamine* was resinified on attempted reduction.



(VII.)



(VIII.)



(IX.)

With a view to a Pschorr synthesis in which the diazo-group should be attached to ring c, 2-nitro-1-naphthylamine was heated with piperonal, but like many other *o*-nitroamines it failed to give a Schiff base.

Elks and Hey (*J.*, 1943, 441) have shown that the triazen $NMe_2 \cdot N{:}N \cdot C_6H_4 \cdot CO_2Me$ yields an *o*-arylbenzoic ester when treated with an aromatic compound under acid conditions. The reaction was applied unsuccessfully to *N*-methylacetnaphthalide in the hope of obtaining the substance (IX) as one product.

Experimental.

Homopiperonylidene-N-*methylhomophthalimide* (III, R = Me).—In preparing homopiperonal from safrole *via* safrole glycol (Erdtman and Robinson, *J.*, 1933, 1530), the safrole was advantageously dissolved in acetone (15 parts) before adding cooled permanganate solution. Homopiperonal (1·8 g.) and piperidine (1 c.c.) were added to *N*-methylhomophthalimide (2 g.) in alcohol (20 c.c.), and solution completed by warming. After 30 minutes the yellow solid (80%) was collected, and its benzene solution passed through a column of alumina. By elution with alcohol, pale yellow *homopiperonylidene*-N-*methylhomophthalimide* was obtained, m. p. 119—130° (Found: C, 70·9; H, 4·9. $C_{19}H_{15}O_4N$ requires C, 71·0; H, 4·7%). Recrystallisation from alcohol or aqueous acetic acid led to great loss, with production of gum. The substance was recovered unchanged after standing for 5 days in chloroform with excess of phosphorus oxychloride; the same reagent undiluted or in boiling toluene, phosphorus pentachloride in chloroform, and phosphoric oxide in benzene failed to cause ring-closure. The double bond was not reduced by hydrogen over palladium or the Adams platinum catalyst in acetic acid or ethyl acetate, even in an all-glass apparatus. Homopiperonylidenehomophthalimide (III, R = H), from homopiperonal (0·5 g.) and homophthalimide (0·5 g.) in alcohol (50 c.c.) with piperidine (6 drops), crystallised from alcohol, had m. p. 195—198°. Purification was difficult, and the crude material could not be cyclised.

Lactone of 1 : 3-*Dihydroxy*-4-*carbethoxy*-2-2'-*carboxyphenylnaphthalene* (V).—Sodium wire (1·3 g.) was added to ethyl homophthalate (5 g.) in ether (25 c.c.) containing alcohol (1 drop), and after 2 days the mixture was heated under reflux for 24 hours. The resulting acidic fraction, treated with a little ether and kept at 0°, afforded the crystalline *lactone* (0·5 g.) which formed colourless needles from acetone, m. p. 181° [Found: C, 71·8, 72·4; H, 3·9, 4·3; *M* (Rast), 315. $C_{20}H_{14}O_5$ requires C, 71·9; H, 4·2%; *M*, 334]. The p-*nitrobenzoate*, prepared in benzene–pyridine, crystallised from acetone in clusters of needles, m. p. 284° (Found: C, 67·2; H, 4·0; N, 3·1. $C_{27}H_{17}O_8N$ requires C, 67·1; H, 3·5; N, 2·9%). The *methyl ether* from the lactone (0·2 g.) in acetone (20 c.c.) with ethereal diazomethane from 4·5 c.c. of nitrosomethylurethane, crystallised from methanol in clusters of needles, m. p. 150° (Found: C, 72·0, 72·7; H, 5·0, 5·0. $C_{21}H_{16}O_5$ requires C, 72·4; H, 4·6%), which dissolved only slowly in warm alkali. The lactone (V), little soluble in cold alkali, dissolved readily on warming to a yellow solution which turned dark red; acidification then afforded a product, orange-brown prisms from alcohol, decomp. above 300° (Found: C, 74·0; H, 4·4%).

Distilled in a stream of hydrogen over zinc dust, the lactone gave a brown gum, which was exhaustively distilled in steam. The volatile *solid* crystallised from methanol–chloroform in leaflets, m. p. 173° (Found: C, 93·8; H, 5·8. $C_{16}H_{12}$ requires C, 94·1; H, 5·9%); although approximating in composition to, it was distinct from, the expected 2-phenylnaphthalene, m. p. 102°. The stable *trinitrobenzene adduct* crystallised from alcohol in light orange leaflets, m. p. 138—140° (Found: C, 53·6; H, 2·9; N, 13·8. $C_{16}H_{12},2C_6H_3O_6N_3$ requires C, 53·3; H, 2·9; N, 13·3%); the unstable *picrate* formed orange microscopic leaflets from alcohol, m. p. 104—114° (Found: C, 52·7; H, 3·0. $C_{16}H_{12},2C_6H_3O_7N_3$ requires C, 50·8; H, 2·7%).

o-Phenacylbenzoic acid (Graebe and Trümpy, *Ber.*, 1898, **31**, 377) melted at 160° (previous softening); 2 : 4-*dinitrophenylhydrazone*, orange-red prisms from ethyl acetate, m. p. 224—225° (Found: N, 13·0. $C_{21}H_{16}O_6N_4$ requires N, 13·3%); *oxime*, colourless needles from ligroin, m. p. 132°, soluble in cold alkali (Found: N, 5·4. $C_{15}H_{13}O_3N$ requires N, 5·5%). The *methyl* ester, prepared by refluxing the dry silver salt with methyl iodide in ether for 1 hour, formed colourless needles, m. p. 114°, from methanol (Found: C, 75·3; H, 5·6. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%); treated with potassium ethoxide (2 mols.) in cold ether–benzene, it afforded a substance, long prisms from much alcohol, decomp. 300°, which gave red solutions in alkali (Found: C, 76·7; H, 3·4%).

The *methyl* ester of *o*-carboxyphenylacetonitrile (Wislicenus, *Annalen*, 1886, **233**, 102), prepared *via* the silver salt, crystallised from ligroin in felted needles, m. p. 47—48° (Found: C, 68·2; H, 5·4. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1%).

2-(3' : 4'-*Methylenedioxybenzyl*)*amino*cyclo*hexanol* (VI, $R_1R_2 = CH_2O_2$).—Methylenedioxybenzylamine (Mannich and Kuphal, *Ber.*, 1912, **45**, 318), b. p. 130—132°/10 mm. (1 g.), and *cyclo*hexene oxide

(*Org. Synth.*, 1925, **5**, 35; 0·65 g.) were heated at 160° (bath-temp.) for 45 minutes and then at 210—220° for 30 minutes. The cyclo*hexanol*, b. p. 175—180°/0·3 mm. (1·5 g.), crystallised from ligroin in long prisms, m. p. 66—67° (Found: C, 67·5; H, 7·7. $C_{14}H_{19}O_3N$ requires C, 67·5; H, 7·6%); *hydrochloride*, rhombic prisms, m. p. 200—201° (previous softening) from 2N-hydrochloric acid (Found: Cl, 12·4; equiv., 284·6. $C_{15}H_{20}O_3NCl$ requires Cl, 12·4%; equiv., 285·5). Boiling for 20 minutes with acetic anhydride containing a drop of sulphuric acid gave the ON-*diacetyl* derivative, hexagonal prisms, m. p. 120°, from ligroin (Found: Ac, 25·7; $C_{14}H_{17}O_3NAc_2$ requires Ac, 25·8%).

A mixture of the base (VI, $R_1R_2 = CH_2O_2$) (5 g.), 90% formic acid (2·2 c.c.), and 35% formalin (2 c.c.) was heated at 100° for 3 hours. The basic fraction, isolated in ether, was dried over potassium hydroxide and distilled; 2-(3′ : 4′-*methylenedioxybenzyl*)*methylamino*cyclo*hexanol*, b. p. 190—200°/0·4 mm., crystallised from ligroin in hexagonal prisms, m. p. 63° (Found: C, 68·3; H, 8·0. $C_{15}H_{21}O_3N$ requires C, 68·3; H, 8·0%); *hydrochloride*, clusters of needles from alcohol–ether, m. p. 160—161° (Found: Cl, 11·7; $C_{15}H_{22}O_3NCl$ requires Cl, 11·8%). Attempted ring-closure with phosphorus oxychloride gave 2-(3′ : 4′-*methylenedioxybenzyl*)*methylamino*cyclo*hexyl chloride hydrochloride*, prisms from alcohol–ether, m. p. 124—125° (Found: Cl′, 11·2; $C_{15}H_{21}O_3NCl{\cdot}Cl'$ requires Cl′, 11·2%).

2-(3′ : 4′-*Dimethoxybenzyl*)*amino*cyclo*hexanol* (VI, $R_1 = R_2 = OMe$), from dimethoxybenzylamine (Juliusberg, *Ber.*, 1907, **40**, 120) and *cyclo*hexene oxide at 200°, formed rosettes of needles, b. p. 185—192°/0·2 mm., m. p. 90° (Found: C, 68·1; H, 8·6. $C_{15}H_{23}O_3N$ requires C, 67·9; H, 8·7%); *hydrochloride*, prisms from alcohol, m. p. 166° (Found: Cl, 11·8. $C_{15}H_{24}O_3NCl$ requires Cl, 11·8%). The N-*methyl* derivative, prepared like its analogue, stout prisms from ligroin, had b. p. 215—220°/0·3 mm., m. p. 66° (Found: C, 68·8; H, 8·9. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0%); *hydrochloride*, prisms from alcohol, m. p. 186—187° (Found: Cl, 11·2. $C_{16}H_{26}O_3NCl$ requires Cl, 11·3%). Treated with acetic anhydride and pyridine at 100°, the secondary base gave the glassy *diacetyl* derivative, b. p. (bath temp.) 180—220°/0·005 mm. (Found: Ac, 24·0. $C_{15}H_{21}O_3NAc_2$ requires Ac, 24·6%); it (1 g.) was kept at room temperature for 2½ hours in a solution of sodium (0·075 g.) in methanol, the exactly neutralised solution evaporated, and the oil taken up in methylene chloride and distilled; this N-*monoacetyl* derivative (0·8 g.) was a gum, b. p. (bath-temp.) 180—190°/0·005 mm. (Found: Ac, 13·9. $C_{15}H_{23}O_3NAc$ requires Ac, 14·0%).

Neither the monoacetyl compound just described nor the secondary and tertiary bases mentioned in the last three paragraphs could be cyclised by treatment with sulphuric acid, phosphoric oxide, phosphorus oxychloride, or phosphorus pentachloride.

6 : 7-*Methylenedioxy*-10-*methylphenanthridone* (VIII).—2-Nitro-4 : 5-methylenedioxybenzoyl chloride (Bedi and Narang, *J. Indian Chem. Soc.*, 1936, **13**, 253) (2·25 g.) was added to methylaniline (1·1 g.) and potassium carbonate (2·2 g.) in ether, and the mixture heated under reflux for 2 hours. 2′-*Nitro*-4′ : 5′-*methylenedioxybenzomethylanilide* (VII) crystallised from alcohol in needles or rhombs, m. p. 145° (Found: C, 60·4; H, 4·2. $C_{15}H_{12}O_5N_2$ requires C, 60·0; H, 4·0%). It absorbed 3 mols. of hydrogen in alcohol over palladium–strontium carbonate; 2′-*amino*-4′ : 5′-*methylenedioxybenzomethylanilide*, which separated from the filtered and concentrated solution, had m. p. 166° after crystallisation from benzene–ligroin (Found: C, 66·4; H, 5·4. $C_{15}H_{14}O_3N_2$ requires C, 66·6; H, 5·2%). Sodium nitrite (0·3 g. in 1·5 c.c. of water) was added to a cooled solution of the base (0·6 g.) in 0·7N-sulphuric acid (10 c.c.), and the mixture heated slowly to 100° until it gave no diazo-reaction. The resulting tar, washed with alkali, crystallised from 80% alcohol in fine needles (0·3 g.), m. p. 238°, as found by Kondo and Uyeo (*loc. cit.*) (Found: C, 71·1; H, 4·4. Calc. for $C_{15}H_{11}O_3N$: C, 71·1; H, 4·3%).

2′-*Nitro*-4′ : 5′-*methylenedioxybenzomethyl*-1-*naphthalide*, prepared like its analogue, formed needles, m. p. 186° (Found: C, 65·3; H, 4·1. $C_{19}H_{14}O_5N_2$ requires C, 65·1; H, 4·0%); hydrogenated in acetone, it gave the *amino*-analogue as needles, m. p. 170° (Found: C, 70·7; H, 5·0. $C_{19}H_{16}O_3N_2$ requires C, 71·2; H, 5·0%). Ring-closure was attempted by diazotisation in aqueous sulphuric, hydrochloric, or acetic acid, or, owing to the low water-solubility of the salts with mineral acids, acetic acid or methanol was used as solvent; decomposition was effected by heating, by treatment with copper powder, or by warming with sodium carbonate or acetate. The acetyl derivative of the amine, m. p. 196°, was treated with " nitrous fumes " in acetic acid, and the crude product heated in benzene or ligroin (cf. Grieve and Hey, *J.*, 1934, 1966). These processes gave brown, amorphous materials, not purifiable by crystallisation, sublimation or chromatography.

2′-*Nitro*-4′ : 5′-*methylenedioxybenzylmethylaniline* was prepared by heating nitromethylenedioxybenzyl chloride (Robinson and Robinson, *J.*, 1915, **107**, 1758) with methylaniline (2 mols.) in benzene for 7½ hours; it was extracted with ligroin from the residue after evaporation of benzene, and crystallised from methanol in yellow plates (70%), m. p. 94° (Found: C, 62·4; H, 5·0. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9%). Reduced over palladium–strontium carbonate in acetone, it gave 2′-*amino*-4′ : 5′-*methylenedioxybenzylmethylaniline* (90%), needles from ligroin, m. p. 118° (Found: C, 70·2; H, 6·1. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·3%); in mineral acids the base turned red and decomposed. With methyl-1-naphthylamine, nitromethylenedioxybenzyl chloride afforded 2′-*nitro*-4′ : 5′-*methylenedioxybenzylmethyl*-1-*naphthylamine*, yellow needles from alcohol, m. p. 133° (Found: C, 67·8; H, 4·7. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8%). Attempted reduction gave only brown basic tars.

Piperonal and 2-nitro-1-naphthylamine failed to react in boiling acetic acid, or alone at 140—160°; a higher temperature caused decomposition.

Acetomethyl-1-naphthalide (8 g.) and 1-*o*-carbomethoxyphenyl-3 : 3-dimethyltriazen (Elks and Hey, *loc. cit.*; 4 g.) were heated at 100° and dry hydrogen chloride passed in; the dark red mixture afforded only acetomethylnaphthalide. Heating the same reactants in acetic acid for 20 hours gave no useful result.

Our thanks are due to the Carnegie Trustees for a scholarship (to H. S. F.), to the Department of Scientific and Industrial Research for a maintenance grant (to A. R. P.), and to the I.C.I. Ltd. (Dyestuffs Division) for financial assistance.

THE UNIVERSITIES OF GLASGOW AND SHEFFIELD. [*Received, December 14th*, 1948.]

NOTES.

New Intermediates and Dyes. Part I. 4-tert.-*Butylphthalic Acid and its Anhydride.*

By R. B. CONTRACTOR and A. T. PETERS.

4-*tert.*-BUTYLPHTHALIC ACID is prepared from 4-*tert.*-butyl-*o*-xylene in 35% yield; this is the first record of an alkylphthalic acid being accessible in reasonable yield, and its reactions are being studied.

The *tert.*-butyl group is resistant to most oxidising agents. Schram (*Monatsh.*, 1888, **9**, 842) stated that *p*-bromo-*tert.*-butylbenzene could be oxidised only with chromic and sulphuric acids, with destruction of the molecule, whilst Verley (*Bull. Soc. chim.*, 1898, **19**, 67) could not completely oxidise di-*tert.*-butylbenzene by any means; Peters (*J.*, 1942, 562) found that the *tert.*-butyl group in *tert.*-butyl- and di-*tert.*-butyl-acenaphthene was resistant to oxidation by a variety of methods. Tsukervanik and Terentieva (*J. Gen. Chem. Russia*, 1937, **7**, 637) recorded that *tert.*-butylnaphthalenes could be orientated by oxidation to the corresponding naphthoic acids by heating with dilute nitric acid in a sealed tube at 150—180° for 15 hours, but Bromby, Peters, and Rowe (*J.*, 1943, 144) failed to effect such oxidation with *β-tert.*-butylnaphthalene, and Gump (*J. Amer. Chem. Soc.*, 1931, **53**, 380) also failed to oxidise di-*tert.*-butylnaphthalene. Bromby *et al.* showed that chromic and acetic acid converted *β-tert.*-butylnaphthalene into 2-*tert.*-butyl-1 : 4-naphthaquinone, and prolonged oxidation of *β-tert.*-butyltetrahydronaphthalene with alkaline permanganate, followed by alkaline peroxide, gave 26·6% of 4-*tert.*-butylphthalic acid.

The authors have now devised a method for preparing 4-*tert.*-butylphthalic acid and its anhydride in 35% yield. 4-*tert.*-Butyl-*o*-xylene (I) was prepared from *o*-xylene, *tert.*-butyl chloride, and zinc chloride; Nightingale and Janes (*J. Amer. Chem. Soc.*, 1944, **66**, 154) found ferric chloride effective. Oxidation of (I) by boiling aqueous potassium permanganate gave 4-*tert.*-butylphthalic acid, readily converted into its anhydride (II).

Condensation of (II) with benzene in the Friedel–Crafts reaction afforded (probably) 2-*benzoyl*-5-tert.-*butylbenzoic acid*, which was readily cyclised by 20% fuming sulphuric acid into *β-tert.*-butylanthraquinone. The latter was identical with that prepared from phthalic anhydride and *tert.*-butylbenzene, followed by ring closure of the resulting 2-(*p-tert.*-butylbenzoyl)benzoic acid (cf. Peters and Rowe, *J.*, 1945, 181), and thus the constitutions of (I) and (II) are confirmed.

Experimental.—4-tert.-*Butyl-o-xylene.*—*tert.*-Butyl chloride (185 g.; 2 mols.) was added gradually to a well-stirred mixture of *o*-xylene (106 g.; 1 mol.) and anhydrous zinc chloride (68 g.; 0·5 mol.) at 70—80° during 10 hours. Fractional distillation of the liquid gave 4-*tert.*-butyl-*o*-xylene as a colourless oil, b. p. 208—211° (102 g.; 63·6%) (Found: C, 88·9; H, 11·0. Calc. for $C_{12}H_{18}$: C, 88·9; H, 11·1%).

4-tert.-*Butylphthalic Acid.*—4-*tert.*-Butyl-*o*-xylene (20 g.) was suspended in water (250 c.c.) in a three-necked flask fitted with a sealed stirrer (quick agitation is necessary), and to the stirred, gently-boiling mixture, an aqueous solution of potassium permanganate (60 g.) was added during 12 hours. Any excess of permanganate was destroyed, sodium hydroxide, (4 g.) was added, and the mixture filtered. Concentration of the filtrate to 100 c.c., followed by acidification wiith hydrochloric acid, gave a sticky solid. The whole was extracted with ether, the ether dried, solvent removed, and the residue boiled with light petroleum (b. p. 60—80°) to give 4-*tert.*-butylphthalic acid, which crystallised from benzene–light petroleum in colourless prisms, m. p. 154° (9·6 g.; 35%) (Found: C, 64·7; H, 6·3. Calc. for $C_{12}H_{14}O_4$: C, 64·9; H, 6·3%).

4-tert.-*Butylphthalic Anhydride.*—The above acid (10 g.) was boiled with acetic anhydride (40 c.c.) for 30 minutes, and the acetic anhydride distilled. The residue crystallised from light petroleum in colourless plates, m. p. 75·5—76·5° (7·8 g.; 84·9%), identical with the anhydride prepared by Bromby *et al.* (*loc. cit.*).

2-*Benzoyl*-5(or 4)-tert.-*butylbenzoic Acid.*—A solution of 4-*tert.*-butylphthalic anhydride (2 g.) in dry benzene (50 c.c.) was treated with anhydrous aluminium chloride (4 g.), and the boiling mixture well stirred for 5 hours. After decomposition by ice-cold hydrochloric acid, and removal of benzene, the residue was extracted with warm aqueous sodium carbonate; acidification of the extract gave 2-*benzyl*-5(or 4)-tert.-*butylbenzoic acid*, which crystallised from chloroform–light petroleum in colourless needles, m. p. 179° (1·7 g.; 61·6%) (Found: C, 76·4; H, 6·4. $C_{19}H_{18}O_3$ requires C, 76·4; H, 6·4%).

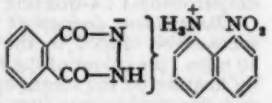
2-tert.-*Butylanthraquinone.*—The foregoing acid (1 g.) was dissolved in fuming sulphuric acid (20%; 6 c.c.) and heated at 100° for 1·5 hours. The mixture was poured on ice, and the precipitate crystallised from methyl alcohol in pale yellow needles, m. p. 104°, not depressed on admixture with 2-*tert.*-butylanthraquinone prepared by the method of Peters and Rowe (*loc. cit.*).—CLOTHWORKERS' RESEARCH LABORATORY, THE UNIVERSITY, LEEDS. [*Received, October 9th*, 1948.]

A Convenient Preparation of 8-*Nitro*-1-*naphthylamine.*

By HERBERT H. HODGSON and JOHN RATCLIFFE.

THE best method extant, from the point of view of yield, for the preparation of 8-nitro-1-naphthylamine is that of Hodgson and Crook (*J.*, 1936, 1844; cf. B.P. 439632), which, however, requires the use of ammonia at 130° under pressure for the hydrolysis of the mixture of 4-, 5-, and 8-nitrophthalo-1-naphthylimides obtained when phthalo-α-naphthalide is nitrated, the amines being subsequently separated by preferential solubilities in 10% aqueous sulphuric acid. An alternative hydrolysis of this mixture by boiling ethanolic hydrazine hydrate at atmospheric pressure is now described, which dispenses with an autoclave, and, by working at a lower temperature, minimises the tar formation to which *peri*-derivatives of naphthalene are prone. From the results, it would appear that the 8-nitrophthalo-1-naphthalide is

preferentially hydrolysed. Since phthalylhydrazide can be extracted by ammonia from the residues, it follows that only the naphthalene portion of phthalo-α-naphthylimide is nitrated.



This work was carried out in 1944—45, and indicates that in the course of the hydrolysis a labile salt (inset) is probably formed, which partly dissociates into its constituents, 8-nitro-1-naphthylamine and phthalylhydrazide, as the reaction proceeds, as shown by increasing development of a red colour. This salt is subsequently decomposed by cold dilute sulphuric acid (cf. Barber and Wragg, *J.*, 1947, 1332).

Experimental.—Phthalo-α-naphthalide, prepared from α-naphthylamine (300 g.), was nitrated according to the procedure of Hodgson and Crook (*loc. cit.*), and the mixture (374 g.) of 4-, 5-, and 8-nitrophthalo-1-naphthylimides so obtained was suspended in ethanol (1 l.) containing hydrazine hydrate (150 c.c.) and boiled under the reflux for *ca.* 1 hour; the minimum reflux period necessary for prevention of tar formation, and consequent loss of 8-nitro-1-naphthylamine, was gauged from the intensity of the deep red colour which develops. The cold mixture was then acidified with aqueous sulphuric acid (50% by volume), the solid filtered off and extracted several times with cold 2N-sulphuric acid (*ca.* 5 l. in all), the extracts combined with the previous filtrate, and the whole basified with aqueous ammonia at 0°; crude 8-nitro-1-naphthylamine (*ca.* 80 g., m. p. 90—93°) was then precipitated; this was purified (70 g., m. p. 93—96°) by extraction with 10% aqueous sulphuric acid, and the extract basified by aqueous ammonia at 0°, the filtered solid being finally crystallised from ligroin; m. p. 96—97° (Hodgson and Crook, *loc. cit.*, and Meldola and Streatfeild, *J.*, 1893, **63**, 1055, give m. p. 96—97°). Phthalylhydrazide was extracted from the final residues by aqueous ammonia, and precipitated from the extract by acidification (m. p. 339°), and recrystallised from ethanol; m. p. 342—345° (lit., 342—346).

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TECHNICAL COLLEGE, HUDDERSFIELD. TECHNICAL COLLEGE OF SOUTH-EAST ESSEX, DAGENHAM.
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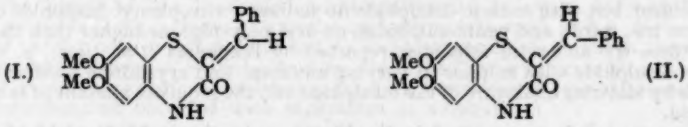
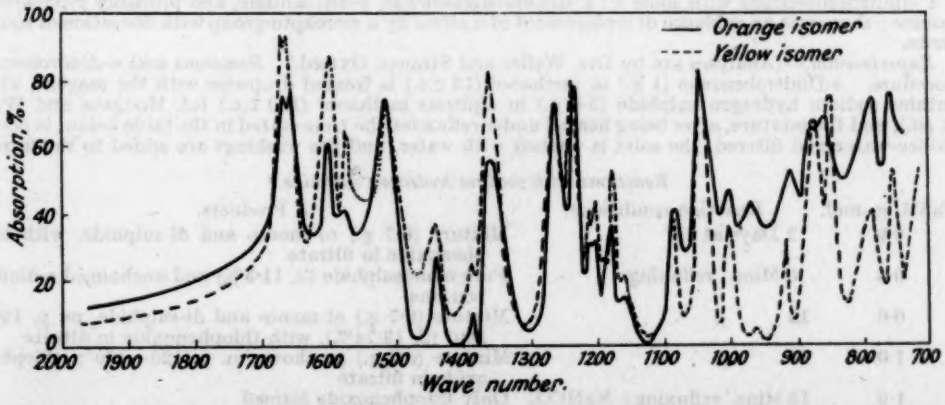
The Benzylidene Derivative of 3-*Keto*-6 : 7-*dimethoxy*-2 : 3-*dihydrobenz*-1 : 4-*thiazine.* By ALEXANDER MACKIE.

3-KETO-6 : 7-DIMETHOXY-2 : 3-DIHYDROBENZ-1 : 4-THIAZINE (Baldick and Lions, *J. Proc. Roy. Soc. New South Wales*, 1937—38, **71**, 113) has been condensed with benzaldehyde and yields two isomeric *benzylidene* derivatives which appear to be *cis*- and *trans*-isomerides, (I) and (II), respectively. Their infra-red



absorption spectra were therefore determined. Inspection of the diagram shows that the absorption bands are identical throughout, but there are marked differences in the intensity of the bands in the two spectra. This substantiates the above suggestion : in all probability the yellow isomer is the *cis*-form, owing to its higher m. p. and greater absorption in the infra-red. Much greater differences in the spectra would be expected if it were a case of keto–enol tautomerism, and both compounds appear to contain a ketonic group. It should be stated, however, that the apparatus used did not allow examination of that end of the spectrum where any hydroxyl groups would appear.



3-Keto-6 : 7-dimethoxy-2 : 3-dihydrobenz-1 : 4-thiazine would not condense with anisaldehyde, 2 : 4-dimethoxybenzaldehyde, *p*-hydroxybenzaldehyde, or *p*-dimethylaminobenzaldehyde.

Experimental.—(Temperatures are uncorrected.) 3-*Keto*-6 : 7-*dimethoxy*-2-*benzylidene*-2 : 3-*dihydrobenz*-1 : 4-*thiazine.* Veratrole (Ullmann, *Annalen*, 1903, **327**, 115) was converted into veratrole-4-sulphonyl chloride (Brown and Robinson, *J.*, 1917, **111**, 953), which was reduced (Fries, Koch, and

Stuckenbrock, *Annalen*, 1929, **468**, 172). From the thiol obtained, 3-keto-6 : 7-dimethoxy-2 : 3 dihydrobenz-1 : 4-thiazine was prepared (Baldick and Lions, *loc. cit.*).

Benzylidene derivatives. Benzaldehyde (2·5 c.c.) and 10% aqueous sodium hydroxide (50 c.c.) were successively added to the ketone (5 g.), dissolved in hot alcohol. The hot mixture was shaken for 10 mins., the colour of the reaction mixture gradually changing to dark red. The reaction was completed by heating on the steam-bath for 45 mins. The alcohol was distilled off till crystallisation commenced, and the residue was then cooled. The orange crystals were filtered off, washed free from alkali, and recrystallised from aqueous alcohol. During the recrystallisation, a yellow residue was found, which was only sparingly soluble in aqueous alcohol. This residue was filtered off, and the filtrate on cooling gave orange needles, m. p. 196—198° (2 g.) (Found : C, 65·6; H, 4·4; N, 4·6. $C_{17}H_{15}O_3NS$ requires C, 65·2; H, 4·8; N, 4·5%). The yellow residue crystallised from absolute alcohol as feathery needles, m. p. 222—223° (1 g.) (Found : C, 65·2; H, 4·8; N, 4·5%).

The two components give different colour reactions with concentrated sulphuric acid, the orange a reddish-brown becoming purple, the yellow an olive-green becoming brown. Both compounds are sparingly soluble in ether, soluble in benzene, acetic acid, and readily soluble in chloroform.

The author's thanks are due to Professor Nisbet for his interest and helpful advice in this work, to Miss J. T. Radford of the Chemical Inspectorate, Ministry of Supply, who carried out the spectrographic work, and to Mr. A. M. Macdonald for the microchemical analyses.—HERIOT-WATT COLLEGE, EDINBURGH. [*Received, November 3rd*, 1948.]

Reactions of Aromatic Nitro-compounds with Alkaline Sulphides. Part II. The Three Dinitrobenzenes.

By HERBERT H. HODGSON and EDWARD R. WARD.

o-DINITROBENZENE reacts with sodium hydrogen sulphide (prepared by the method of Hodgson and Ward, *J.*, 1948, 242) in aqueous methanol to give sodium *o*-nitrothiophenoxide, 2 : 2′-dinitrodiphenyl sulphide by subsequent reaction between this product and *o*-dinitrobenzene, and 2 : 2′-dinitrodiphenyl disulphide, formed probably by oxidation of the above thiophenoxide by the concurrently liberated sodium nitrite (cf. the use of sodium nitrite in the manufacture of sulphur dyes). When about 0·4 g.-mol. of reducing agent is used per g.-mol. of *o*-dinitrobenzene, only the monosulphide is obtained, but with more of the reagent both mono- and di-sulphide are formed, and excess reduces the disulphide to thiophenoxide. The amounts of the products vary according to temperature, time of reaction, alkalinity, quantity of reagent, and rate of its addition; the presence of sodium hydrogen carbonate favours the formation of thiophenoxide rather than of disulphide.

The results of Blanksma and his co-workers with sodium sulphide (*Rec. Trav. chim.*, 1901, **20**, 115) have been confirmed, but with sodium disulphide no sodium *o*-nitrophenyl disulphide could be identified, and with sodium tri-, tetra-, and penta-sulphides, no aryl polysulphide higher than the disulphide could be prepared; these tri- and tetra-sulphides, reported by Blanksma *et al.* (*ibid.*, p. 144), appear to be mixtures of the disulphide with sulphur in varying amounts, and crystalline products resembling them have been made by allowing a mixture of the disulphide and the requisite amount of sulphur to crystallise from acetic acid.

The many previous failures reported in the literature to obtain 100% yield of *m*-nitroaniline by reduction of *m*-dinitrobenzene with alkaline sulphides would appear to be due to concurrent formation of *m*-phenylenediamine, and its subsequent interaction with the sodium thiosulphate always present in alkaline sulphide reductions (cf. Bernthsen's thiosulphate process for methylene-blue). Sodium hydrogen sulphide in hot aqueous methanol is now found to give 90—95% yields of *m*-nitroaniline free from azoxy-compound even under ice-cold conditions, thiophenoxide and consequent accompaniment of sodium nitrite not being observed.

p-Dinitrobenzene reacts with sodium hydrogen sulphide in aqueous methanol to give mainly 4 : 4′-dinitroazobenzene with some 4 : 4′-diaminoazobenzene, *p*-nitroaniline, and probably *p*-phenylenediamine; there was no evidence of replacement of a nitro- by a mercapto-group with liberation of sodium nitrite.

Experimental.—(Analyses are by Drs. Weiler and Strauss, Oxford.) *Reactions with o-dinitrobenzene.* Procedure. *o*-Dinitrobenzene (1 g.) in methanol (15 c.c.) is treated dropwise with the reagent, which contains sodium hydrogen sulphide (3·6 g.) in aqueous methanol (100 c.c.) (cf. Hodgson and Ward, *loc. cit.*), and the mixture, after being heated under reflux for the time stated in the table below, is poured into ice-water and filtered, the solid is washed with water, and the washings are added to the filtrate.

*Reactions with sodium hydrogen sulphide.**

NaSH, g.-mol.	Reaction conditions.	Products.
0·9	2 Days at 15°	Mixture (0·7 g.) of mono- and di-sulphide, with thiophenoxide in filtrate
0·4	5 Mins.' refluxing	Pure monosulphide (S, 11·3%) and unchanged *o*-dinitrobenzene
0·6	15 ,,	Mixture (0·7 g.) of mono- and di-sulphide, m. p. 120—160° (S, 13·74%), with thiophenoxide in filtrate
1·0	15 ,,	Mixture (0·3 g.) as above, m. p. 120—160°; thiophenoxide in filtrate
1·0	15 Mins.' refluxing; $NaHCO_3$ (0·25 g.) present	Only thiophenoxide formed
0·9	15 Mins.' refluxing, but nitro-compound added to reagent	Pure disulphide (0·35 g.) with thiophenoxide in filtrate

* Monosulphide refers to 2 : 2′-dinitrodiphenyl sulphide (m. p. 122°; S, 11·6%), and disulphide to 2 : 2′-dinitrodiphenyl disulphide (m. p. 197°; S, 20·8%).

Reactions with sodium mono-, di-, tri-, tetra-, and penta-sulphide.

Reagent (g.; g.-mol.).	Reflux period, mins.	Products.
Na_2S (0·25; 0·5)	15	Immediate intense blue colour followed by slow formation of monosulphide (0·8 g.) (S, 11·7%)
Na_2S_2 (0·36; 0·5)	15	Disulphide (0·8 g.), m. p. 193—194°; recrystallised from glacial acetic acid, m. p. 196—198° (Blanksma, *loc. cit.*, gives m. p. 195°) (Found: S, 21·0%)
Na_2S_3 (0·5; 0·7)	15	Pure disulphide, after addition of iodine (1 g.) in methanol to filtrate
Na_2S_3 (0·43; 0·5)	5	Yellow crystalline precipitate (1 g.), m. p. 178—182°; recrystallised from glacial acetic acid, m. p. 187—188°. Crude product (S, 37·8%)
Na_2S_4 (0·55; 0·5)	5	Yellow crystalline product (2 g.), m. p. 184—185°
Na_2S_5 (0·6; 0·5)	5	Yellow crystalline product (2·2 g.), m. p. 180—183°; recrystallised from glacial acetic acid, m. p. 186—188° (S, 45·51%)

The products from sodium tri-, tetra-, and penta-sulphides after extraction with carbon disulphide had m. p.s 197—198°, 195—197°, and 195—198°, with sulphur contents of 22·0, 21·0, and 21·2%, respectively, and were thus almost pure 2 : 2′-dinitrodiphenyl disulphide (S, 20·8%). When amounts of the pure disulphide (m. p. 195—197°) and sulphur were dissolved in the minimum amount of boiling glacial acetic acid in g.-mol. ratios of 1 : 1 and 1 : 3, the solutions on cooling deposited products of m. p. 184—190° (S, 32·0%) and 170—185° (S, 40·6%), respectively.

Reactions with m-*dinitrobenzene.* *m*-Dinitrobenzene (10 g.) in methanol (75 c.c.) was heated under reflux for 15 minutes with sodium hydrogen sulphide (5·5 g. in 140 c.c. of aqueous methanol; theory for complete reduction to *m*-nitroaniline is 5 g.) and then heated for a further 10 minutes, and the methanol removed by distillation (150 c.c.); the mixture when added to ice-water (500 g.) gave a precipitate of *m*-nitroaniline (8·3 g., >90% yield). When a deficiency of sodium hydrogen sulphide (*ca.* 4 g.) was used, the yield of *m*-nitroaniline (6·5 g.) decreased and it was mixed with unchanged *m*-dinitrobenzene.

Reactions with p-*dinitrobenzene.* *p*-Dinitrobenzene (5 g.) in methanol (75 c.c.) is treated dropwise for 10 minutes under reflux with sodium hydrogen sulphide (1 g.) in methanol (15 c.c.) and water (10 c.c.). The initial red colour preceded a dark red precipitate and, after a further 5 mins.' heating, the mixture is added to ice-water (150 c.c.) and filtered; the residue is steam-distilled to remove unchanged nitro-compound and then is found to be 4 : 4′-dinitroazobenzene (1·35 g.; m. p. 222°). Concentration of the filtrate to 75 c.c. afforded *p*-nitroaniline (0·5 g.; m. p. 142—144°). With more sodium hydrogen sulphide (1·5 g.), there is no unchanged nitro-compound, and 4 : 4′-dinitroazobenzene (2·5 g.) is obtained, whilst both *p*-nitroaniline and 4 : 4′-diaminoazobenzene are in the filtrate.

When 4 : 4′-dinitroazobenzene or *p*-dinitrobenzene was heated under reflux with a solution of sodium thiosulphate (5 g.) in methanol (40 c.c.) and water (10 c.c.), there was no loss of azo-compound, but a 25% loss of *p*-dinitrobenzene occurred with separation of sulphur.

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Three- and Four-membered Heterocyclic Rings.

THE TILDEN LECTURE, DELIVERED AT THE ROYAL INSTITUTION, LONDON, ON JANUARY 20TH, 1949, AND IN NEWCASTLE ON JANUARY 28TH, 1949.

By F. E. KING, M.A., D.Phil., D.Sc.

THE 3- and 4-membered rings, with their unique stereochemical problems and exceptional reactivity, have remained since the days of their discovery in the 1880's one of the most attractive themes in Chemistry. Under the stimulus afforded by the researches of the younger W. H. Perkin, the early history of this subject is chiefly concerned with the carbocyclic compounds, and, although the smaller heterocyclic systems were also well known at the beginning of the century, their derivatives were not so closely or consistently studied.

For several reasons this group of heterocyclic compounds has in more recent times begun to attract wider attention, and in view of its growing importance it seemed of interest to summarise progress in this division of chemistry. It was soon evident, however, on undertaking a survey of the literature, that the 3- and 4-membered heterocyclic compounds were already far too numerous to be covered in a single lecture, and it has been necessary to limit the types to be discussed. The group which has been selected for review consists of the smaller rings containing a single atom of nitrogen as the hetero-element, *i.e.*, the ethylene- and trimethyleneimines, and the corresponding lactams and imides.

Cyclic Imines.

From the ease of formation of pyrrolidine and piperidine rings on the one hand, and of the analogous *cyclo*paraffins on the other, it may be assumed that, on substituting the hetero-atom for one of the carbons of the 3- and 4-membered homocyclic structures, no new stereochemical factor will be introduced. According to the general principles of ring-formation as stated by Ruzicka,[1] the preponderating effect of the more favourable " distance factor " should cause ethyleneimine (aziridine) to be somewhat more readily synthesised than trimethyleneimine (azetidine), though neither would be expected to be formed with the ease of their higher homologues, pyrrolidine and piperidine.

This conclusion cannot be verified, as can sometimes be done in the carbocyclic series, by comparing the relative yields of the various cyclic imines, since the necessary data do not exist. The 38% of ethyleneimine obtained by distilling a mixture of 2-bromoethylamine hydrobromide and strong aqueous potassium hydroxide—the original method of preparation [2]—is of the undried base, b. p. 54—67°; the yield of trimethyleneimine from the 3-bromopropylamine hydrobromide [3] has not been recorded. Ladenburg's synthesis, viz., pyrolysis of the alkylenediamine hydrochlorides, gives an unknown but evidently limited yield of trimethyleneimine,[4] and does not succeed with ethylenediamine (which affords piperazine).[5] The remaining preparation of trimethyleneimine is from toluene-*p*-sulphonyltrimethyleneimide, formed with its 8-ring dimer from trimethylene bromide, toluene-*p*-sulphonamide, and alkali; the imine is then obtained by sodium–amyl alcohol reduction.[6] The original paper does not state the amounts obtained, and the sole recorded figures (39% and 14%), which are from recent work,[7, 8] refer only to the second stage of the synthesis.

The corresponding ethylenesulphonimide has not been prepared, except as a derivative of the already formed imine, although the syntheses of some substituted 3-ring sulphonimides from open-chain compounds have been described.[9] Whether reductive fission of the sulphonyl group is possible is not known, but there is evidence in the hydrogenolysis of toluene-*p*-sulphonyl-2-phenylethyleneimide to phenylethylamine or its sulphonamide [10] and of 2 : 2-dimethylethyleneimine to *tert.*-butylamine,[11] that it would lead to destruction of the imine ring.

Fortunately, the bromo-amines readily undergo intramolecular condensation in dilute solutions at ordinary temperatures, so that accurate measurements of the velocity of the reaction can be made. The velocity constants at 25°, determined by Freundlich and Salomon,[12] are shown in Table I, and they give convincing proof to Ruzicka's theory of ring formation in its application to the cyclic imines.

The rate of cyclisation to ethyleneimines is generally increased, sometimes very markedly, by the presence of substituents. This is strikingly shown by the following data collected by Salomon,[13] on the ring-closure of some 2-chloroethylamines.

TABLE I.

Ring-closure constants ($t = 25°$): effect of chain length.

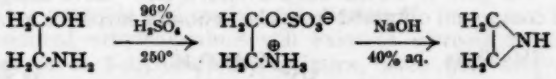
		k.
$Br·[CH_2]_2·NH_2$	Ethyleneimine	0·036
$Br·[CH_2]_3·NH_2$	Trimethyleneimine	0·0005
$Br·[CH_2]_4·NH_2$	Pyrrolidine	*ca.* 30
$Br·[CH_2]_5·NH_2$	Piperidine	0·5

TABLE II.

Ring-closure constants ($t = 25°$): effect of substituents.

	k.		k.
$Cl·CH_2·CH_2·NH_2$	0·0005	$Cl·CHMe·CH_2·NH_2$	0·002
$Cl·CHPh·CH_2·NH_2$	0·4	$Cl·CH_2·CHMe·NH_2$	0·015
$Cl·CH_2·CHPh·NH_2$	*ca.* 0·0003		

The study of the ethyleneimines was greatly assisted when ethanolamine and some of its homologues became available as technical products. From these the chloroethylamines are then readily obtained by the action of thionyl chloride, and improved methods of treating the chloro-compounds with alkalis have led to high yields of the cyclic bases, 60—70% over-all in the case of ethyleneimine.[14] A useful contribution was made in 1935 by Wenker,[15] who found that ethyleneimine is very conveniently prepared from ethanolamine through the sulphuric ester-salt:



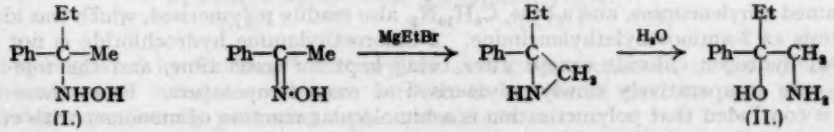
This synthesis is particularly successful for some of the *C*-alkylethyleneimines, as shown by the following data due to G. D. Jones:[8]

Ethanolamine.	Imine.	Yield.	B. p.
$HO·CH_2·CH_2·NH_2$	Ethyleneimine	32%	55—56°
$HO·CHMe·CH_2·NH_2$	2-Methylethyleneimine	65%	63—64°
$HO·CH_2·CHEt·NH_2$	2-Ethylethyleneimine	46%	88—89°
$HO·CHMe·CHMe·NH_2$	2 : 3-Dimethylethyleneimine	47%	65—77° (mixed isomers)
$HO·CH_2·CMe_2·NH_2$ *	2 : 2-Dimethylethyleneimine	68%	69—70°
$HO·CHMe·CMe_2·NH_2$	2 : 2 : 3-Trimethylethyleneimine	19%	83—85°
$HO·CHPr·CMe_2·NH_2$	2 : 2-Dimethyl-3-*n*-propylethyleneimine	57%	128—129°

* $HO·CMe_2·CH_2·NH_2$ does not give 2 : 2-dimethylethyleneimine.[16]

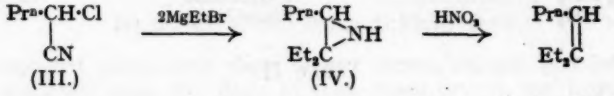
The aryl-substituted ethanolamines cannot be cyclised in this way, as they are too readily dehydrated, giving vinylamines which then resinify. The preparation of trimethyleneimines by the Wenker method has apparently not been investigated.

A remarkable synthesis of the aziridine ring occurs when alkyl- or aryl-magnesium halides react with the aryl alkyl ketoximes.[17] The reaction appeared to be of use for the preparation of substituted hydroxylamines, *e.g.*, (I), but the supposed hydroxylamines proved to be ethanolamines (II) arising from the primary products, the ethyleneimines, which were then isolated in good yield by modifying the experimental procedure:

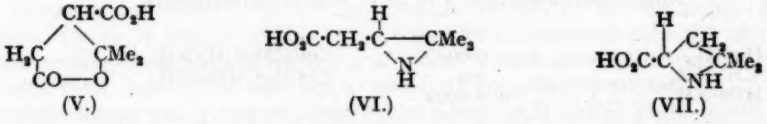


As is well known, the valency distortion consequent on the formation of the smaller imine rings gives them abnormal reactivity; this is especially marked with ethyleneimines owing to the small dimensions of the 3-membered ring. Freundlich and Neumann[18] have shown that the reaction, $Br·CH_2·CH_2·NH_2 = (CH_2)_2NH,HBr$, is quantitatively reversed in hydrobromic acid solution, and have measured the velocity of the change. Trimethyleneimine has long been known to undergo a similar change, in warm dilute hydrochloric acid, to 3-chloropropylamine hydrochloride,[8] but there are no data from which a quantitative comparison with

ethyleneimine can be made. The greater acid-stability of the 4-ring base is evident, however, in its reaction with nitrous acid to form *N*-nitrosotrimethyleneimine, whereas the fragility of the ethyleneimine ring precludes the formation of nitroso-compounds. Reaction with nitrous acid may therefore sometimes serve as a means of identifying ethyleneimines, for example, the imine (IV) synthesised from the α-chloro-nitrile (III) and ethylmagnesium bromide : [19]



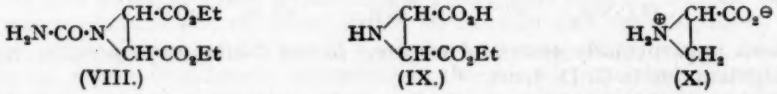
(III.) (IV.)



(V.) (VI.) (VII.)

Of the two structures suggested by Corselli [20] for the product obtained on heating terebic acid (V) with alcoholic ammonia, the ethyleneimine (VI) can at once be rejected since the compound gives a crystalline nitroso-derivative. On the other hand, from the stability of the substance to acids, the alternative constitution (VII) is also very improbable.

The existence of ethyleneimine-carboxylic acids has never definitely been established; compounds obtained from ethyl dibromosuccinate and ammonia, and described in the early literature as cyclic imines, are most probably derivatives of aminofumaric (iminosuccinic) acid. A more recent example, to which Curtius and Dörr [21] have assigned the constitution (VIII), is the principal compound obtained from the action of carbamic azide on ethyl fumarate.



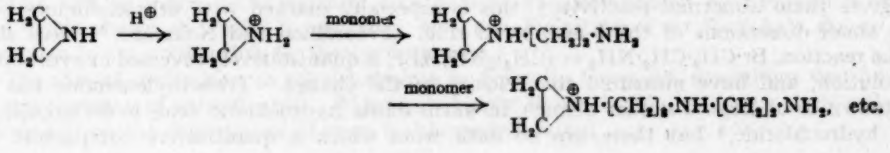
(VIII.) (IX.) (X.)

Its hydrolysis product, regarded as (IX), has m. p. 73° and is thus not identical with the corresponding half ester (m. p. 98°, 100°) originating from ethyl dibromosuccinate, but the cyclic nature of these substances has since been disputed.[22] Compounds of this series would almost certainly be internal salts, as in (X); in view of the instability of the ethyleneimmonium ion, it is unlikely that the ethyleneimino-acids could be isolated.

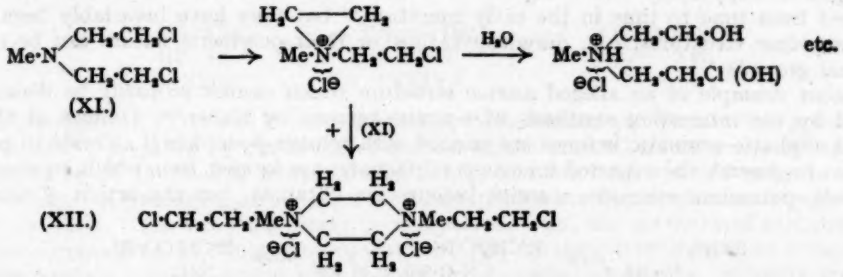
The most important feature of the ethyleneimines, and to a limited extent of trimethyleneimine, is their ability to undergo additive polymerisation when catalysed by acids (including CO_2). In this, ethyleneimine behaves as if it were the unknown vinylamine, $H_2C{:}CH{\cdot}NH_2$, the constitution attributed to the base by its discoverer Gabriel, until the sulphonamides were found by Marckwald [23] to be alkali-insoluble.

In the last 10—12 years a considerable patent literature has accumulated covering not only polymerisation, but also crossed polymerisations of ethyleneimine with halogenated paraffins, saturated and unsaturated organic acids, *iso*cyanates, *iso*thiocyanates, carbon disulphide, sulphur chloride, mercaptans, etc., to give numerous products of potential value in rubber, paint, leather, and petroleum technology, and in the various ramifications of the plastics industry. Obviously, these phases of the subject are far too vast for description here.

G. D. Jones *et al.*[24] have investigated the mechanism of ethyleneimine polymerisation by observing the behaviour of the imine with hydrochloric acid in ether and in aqueous solution. On adding the solid freshly precipitated from ethereal hydrogen chloride to alkali, there were obtained ethyleneimine, and a base, $C_4H_{10}N_2$, also readily polymerised, which was identified by synthesis as 2-aminoethylethyleneimine. 2-Chloroethylamine hydrochloride is not formed in ethereal hydrogen chloride except after being kept for some time, and the free chloroamine is only comparatively slowly polymerised at room temperature. From these observations it is concluded that polymerisation is a bimolecular reaction of monomer with ethyleneimmonium (and then substituted immonium) ions, which can be represented as follows :



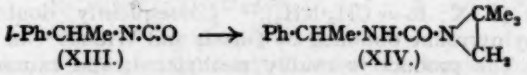
The formation of cyclic ethyleneimmonium salts was the subject of detailed investigation during the late war as it is closely bound up with the chemistry of the "nitrogen mustard gases." * Methylbis-2-chloroethylamine (XI), for example, undergoes dimerisation—which can be very rapid in alcohol—to the dipiperazinium salt (XII), and it is also slowly hydrolysed in contact with water. These reactions have been found to depend on an initial cyclisation to the 2-chloroethylimmonium salt: [26]



3-Bromopropylamines, $Br{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NR_2$ (R = Et, Pr^n, Bu^n), also undergo condensation when allowed to stand without a solvent or in concentrated solution, forming quaternary salts with 4-ring structures, but the dimethylamino-base gives a linear polymer. A monomeric quaternary salt can be obtained if the dimethylaminopropyl bromide is left in dilute (0·01M.) ethanol solution, but it is unstable and readily polymerises.[27]

Many of the substituted ethyleneimines will exist in stereoisomeric forms. There are two such modifications of 2 : 3-diphenylethyleneimine, *meso* (*cis*) and racemic (*trans*), but optically-active ethyleneimines can only be prepared by ring-closure of the active 2-chloroethylamines,[28] and have never been obtained by resolution at the imine stage. On the other hand, several independent attempts were made about 10 years ago to prepare and resolve 2 : 2-disubstituted ethyleneimines in the hope of obtaining products in which optical activity would be due to asymmetry of the tervalent nitrogen atom; the subject was well reviewed at the time by Maitland.[29] The expectation that ethyleneimines would be resolved is based on the view that the 3-membered cyclic imines afford the nearest approach among saturated nitrogen compounds to the strained >C═N− group of the oximes, etc., which owe their geometrical isomerism to its non-planar structure. At the time these attempts were made, the stability of the separate pyramidal forms of the nitrogen in the ethyleneimine ring was merely a plausible supposition. However, later calculation from spectroscopic data [30] shows that the activation energies of racemisation for the stereoisomeric forms of a given ethyleneimine are considerably above the minimum value necessary for stability, so that the project now has secure theoretical foundation.

In the attempted resolution, salt formation with the imino-group must, of course, be avoided, or the nitrogen atom will lose its asymmetry through the formation of an immonium ion, $>\overset{\oplus}{N}HR$. Of the methods employed, the condensation of an optically active *iso*cyanate (XIII) with 2 : 2-dimethylethyleneimine is a later example,[31] but fractional crystallisation of the product (XIV) gave no evidence of separation into isomers.



It has been suggested by Pauling [32] that aryl or acyl groups attached to the nitrogen may inhibit the resolution owing to resonance between the unshared electrons and the adjacent unsaturated groups, thereby producing a planar molecule.

Unsaturated Cyclic Imines.

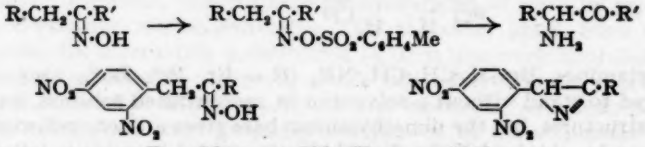
The inclusion of a double bond in the 3- and 4-membered rings will obviously add considerably to their instability. The strain factor will be especially high in the 3-ring (azirine); not only may the unsaturated link be expected to increase the tendency to self-condensation, but, if the unsaturation is situated between nitrogen and carbon—implying Schiff's base

* Ethyleneimine is itself an active vesicant.[25]

properties—the molecule may be even more labile. These characteristics, on the whole, would be less pronounced in the 4-membered azetine ring, and it is conceivable that this might have a certain measure of stability. These conclusions are supported by analogies in the carbocyclic series, where the existence of the 3-membered *cyclo*propene ring is generally considered to be improbable. *cyclo*Butene, on the other hand, is a fully authenticated hydrocarbon prepared by Willstätter in the experiments on *cyclo*butadiene.[33]

Compounds supposedly containing the unsaturated 3-membered azirine nucleus have been mentioned from time to time in the early literature,[34] but they have invariably been shown to possess other structures, *e.g.*, dihydropyrazine, or their polymeric nature can be inferred on general grounds.

A recent example of an alleged azirine structure which cannot so easily be dismissed is provided by the interesting synthesis of α-amino-ketones by Neber.[35] Oximes of aliphatic or mixed aliphatic–aromatic ketones are treated with toluene-*p*-sulphonyl chloride in pyridine solution. In general, the expected toluene-*p*-sulphonates are formed, from which, by dissolution in alcoholic potassium ethoxide, α-amino-ketones are obtained, but the action of toluene-*p*-

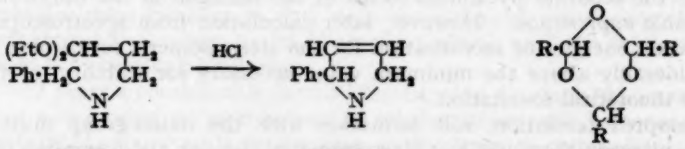


(XV.) (XVI.)

R = Me, m. p. 79°; Ph, m. p. 100°.

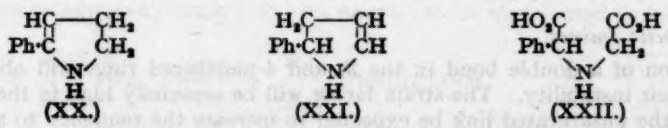
sulphonyl chloride and pyridine on the oximes (XV; R = Me) and (XV; R = Ph) gives salts of amines to which cyclic imine structures (XVI) have been ascribed. Analyses, and in one instance (XVI; R = Me) molecular-weight estimations, attest the molecular formulæ of the compounds, from both of which under suitable acid conditions the expected α-amino-ketones were then obtained.

No authentic examples of the unsaturated 4-membered azetine nucleus can be traced, though it might be supposed that a ring system of this kind would result from the intramolecular condensation of β-amino-aldehydes or -ketones. The self-condensation of β-amino-aldehydes leads generally to polymers,[36] but there existed an apparent exception in the cyclisation of β-benzylaminopropaldehyde diethyl acetal (XVII) in cold hydrochloric acid to the hydrochloride of the Δ^3-phenylpyrroline (XVIII).[37]



(XVII.) (XVIII.) (XIX.)

Re-examination showed that the product did not possess the properties of a pyrroline; a 4-ring structure therefore seemed possible, but was disproved when the base was found to be a trimer (XIX; R = $CH_2 \cdot CH_2 \cdot NH \cdot CH_2Ph$) [74] similar in constitution to the trimer of α-aminoacetaldehyde (XIX; R = $CH_2 \cdot NH_2$).[38] Consequently, doubt arises as to the constitution of the phenylpyrroline obtained by Gitsels and Wibaut [39] in 1941 from the reduction of 2-phenylpyrrole. The product is readily methylated, and cannot therefore be a Δ^1-(or Δ^5-)pyrroline. 2-Phenyl-Δ^2-pyrroline (XX) had already been unambigously synthesised,[40] and the apparent exclusion of the Δ^3-isomer (XVIII) had therefore left only (XXI) for the structure of the new pyrroline.

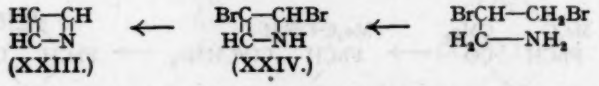


(XX.) (XXI.) (XXII.)

The supposed Δ^4-pyrroline has now been oxidised with ozone and hydrogen peroxide, but, instead of the expected product (β-amino-β-phenylpropionic acid), the known *N*-α-carboxy-

benzylglycine (XXII) was isolated.[74] The reduction of 2-phenylpyrrole is therefore analogous to that of pyrrole itself in giving the Δ^3-compound, and the Δ^4-phenylpyrroline is for the present unknown.

The non-existence of azirine and of azetine would seem to exclude all possibility of still more highly unsaturated structures such as (XXIII), although, as W. Baker [33] has suggested with reference to the yet unknown *cyclo*butadiene, the increased angular strain of aza-*cyclo*butadiene might in some degree be compensated by resonance.

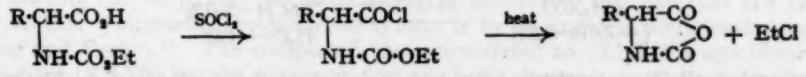


(XXIII.) (XXIV.)

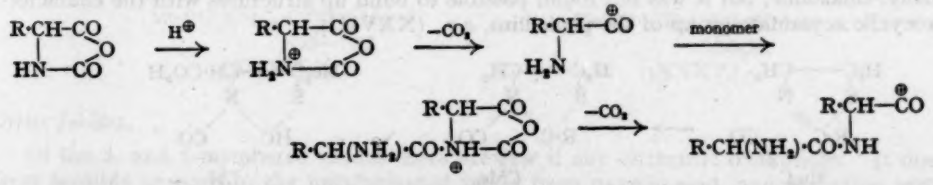
The structure (XXIII) was in fact assigned by Abderhalden and Paquin [41] to a volatile base (" pyriculine ") prepared by the action of sodium on the ethereal solution of a dibromo-amine believed to be (XXIV). The hydrobromide of this dibromo-base was said to be precipitated, with evolution of hydrogen, on leaving a solution of 2 : 3-dibromopropylamine in ether to stand for several days. The work has lately been repeated,[42] and the precipitated salt shown to be the hydrobromide of 2 : 3-dibromopropylamine; the bromine-free compound obtained from the intermediate dibromo-amine with sodium is, of course, allylamine, formerly obtained in this way by Paal.[43] The 2-methylpyriculine of Oesterreich,[44] prepared from 2 : 4-dimethyl oxazole and acetaldehyde, may in all probability also be discounted.

Lactams.

The recent accelerated growth in the hitherto limited field of the lower cyclic amides is a result of the interest in the chemistry of the penicillins, as in this group of substances there is recorded for the first time the natural occurrence of a β-lactam structure. The simplest possible cyclic amides, the α-lactams, do not exist; as a result of the over-riding tendency to form either diketopiperazines or chain condensates,[45] cyclic intramolecular anhydrides of the α-amino-acids have never been observed. Yet, their synthesis deserves attention, since, by a process similar to that which leads to polymethyleneimines, products of a polypeptide structure should become available. Synthetic substances of this type are already known, having been obtained from the anhydrides of *N*-carboxyamino-acids first synthesised by Leuchs.[46]

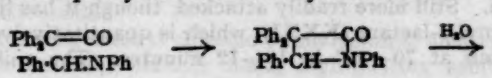


Thesė anhydrides may be recrystallised, but, if left in moist air or solvents, or in contact with any substance able to liberate protons, loss of carbon dioxide occurs, accompanied by chain polymerisation :

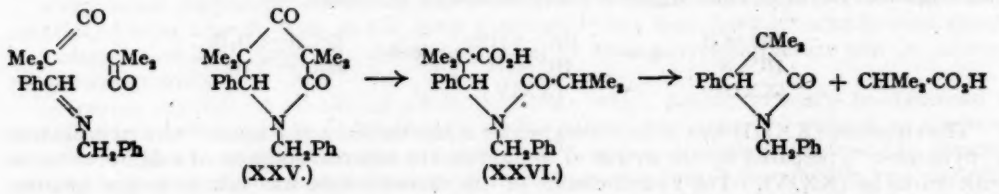


With the development of polymer chemistry, this reaction has acquired a new significance, and, in addition to the earlier experiments, the copolymerisation of carboxyanhydrides has now been investigated.[47] The Leuchs synthesis of peptides might be expected to give some monomeric compounds, but there is no evidence that they are present in the reaction products. It is possible that they may be obtainable under other experimental conditions, if the 3-ring structure is not rendered too unstable by resonance in the amide group.

Although there is at least one earlier reference to β-lactams,[48] these compounds were virtually unknown until Staudinger's synthesis of the lactam of β-anilino-ααβ-triphenyl-propionic acid from diphenylketen and benzylideneaniline.[49]



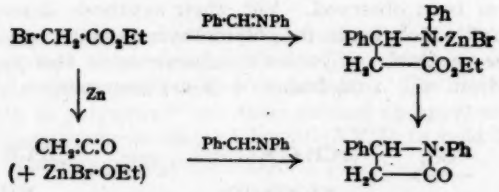
The constitution of this and similar products was confirmed by hydrolysis to the amino-acids. Some of the β-amino-acids have been recyclised to lactams by acid chlorides,[50] but it is a method of limited application. Not infrequently, *e.g.*, with dimethylketen, piperidinediones (XXV) are obtained, formed from two molecules of the keten and one of Schiff's base. However, they are readily hydrolysed to acylamido-compounds (XXVI), and, when these are heated, the β-lactam ring is sometimes closed by loss of aliphatic acid.



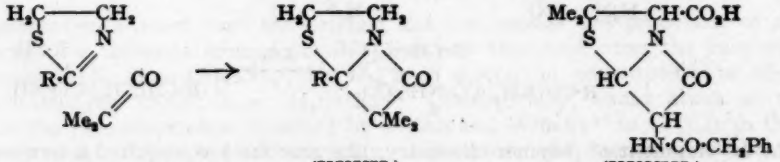
(XXV.) (XXVI.)

A further means of cyclising β-amino-acids was described by Breckpot in 1923,[51] depending on the action of the organomagnesium halides on their esters. From the ethyl esters of β-ethylamino- and β-methylamino-*n*-butyric acid and ethylmagnesium bromide, the corresponding β-lactams were isolated in low yields as distillable oils, of which the latter was hydrolysed to the amino-acid with concentrated hydrochloric acid. The application of this reaction to α-amino-esters, as a means of obtaining α-lactams, is being investigated.

1 : 4-Diphenylazetidinone, obtained by Staudinger from keten and benzylideneaniline,[52] was also synthesised by Gilman and Speeter [53] from the Schiff's base, ethyl bromoacetate, and zinc in boiling toluene. This condensation has been represented as a further example of the Reformatsky reaction, but it may be no more than a convenient modification of the Staudinger synthesis with the keten formed *in situ*. With the bromoacetic ester the method gives 56% of lactam, and with ethyl α-bromopropionate 85%.



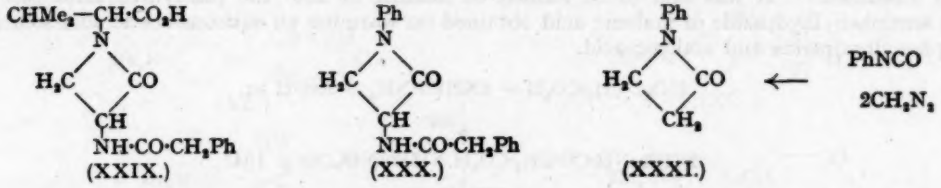
Adaptations of all these methods have been applied to the synthetical problems of penicillin chemistry, and they are extensively discussed elsewhere.[54] The results were disappointing; crystalline compounds containing the fused thiazolidine-β-lactam structure (XXVII) were obtained by condensing dimethyl- or diphenyl-keten with the >C═N– link of 2-methyl- or 2-phenyl-thiazoline, but it was not found possible to build up structures with the characteristic exocyclic acylamido-group of the penicillins, *e.g.*, (XXVIII).



(XXVII.) (XXVIII.)

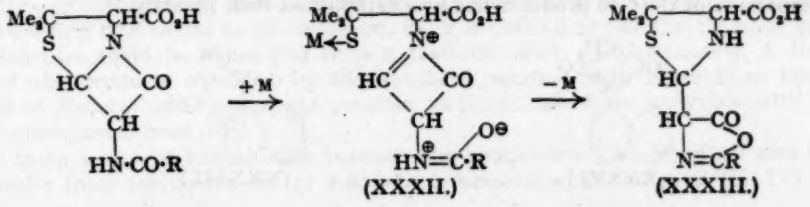
The outstanding characteristic of the chemistry of the penicillins—in which they contrast sharply, not only with the purely synthetic β-lactams, but also with dethiobenzylpenicillin (XXIX)—is the instability of the β-lactam ring. The tetraphenylazetidinone of Staudinger is extraordinarily difficult to hydrolyse; resistance to alkali is much less marked when features of the penicillin structure are present, as in the fused thiazolidine-β-lactams just mentioned, and in the acylamido-β-lactam (XXX) which requires approximately 1½ hours at 100° for complete hydrolysis with N-alkali. Still more readily attacked, though it has little in common with the penicillins, is the *N*-phenyl-β-lactam (XXXI), which is quantitatively converted into β-anilinopropionic acid by N-alkali at 70—80° in 10—12 minutes. The anilinopropionic-β-

lactam, a readily-soluble crystalline solid, m. p. 78—79°, is a recent addition to the series;[55] its preparation from phenyl *iso*cyanate and diazomethane is reminiscent of the synthesis



of *cyclo*butanone from diazomethane and keten. It is probably one of the simplest β-lactams yet known; the product obtained by Delépine[56] from the permanganate oxidation of one of the tricrotonylidenetetra-amines is too insoluble and inert to be the monomeric lactam of β-aminobutyric acid, though it forms this compound on vigorous hydrolysis.

Chain[57] has shown that the biological inactivation of the penicillins, *e.g.*, by methanol, is catalysed by traces of metals (copper, zinc, tin), and suggests that under the influence of adventitious traces of these elements it is the thiazolidine ring and not the lactam which is first broken. This leads to a strained, and hence highly reactive structure (XXXII), which by well-known electronic displacements re-arranges into an oxazolone (XXXIII). The metal atom is simultaneously transferred to another molecule, and re-formation of the thiazolidine ring follows. The various reactions by which the penicillins are so readily inactivated can then be expressed in terms of the well-established lability of the saturated oxazolone ring:



Before leaving the subject of the β-lactams, it is interesting to recall that one of the first references to this 4-membered heterocyclic system is to be found in some early experiments by Kipping and Perkin.[58] The compound they formulated as (XXXIV) was obtained from the diketo-ester (XXXV) by the action of cold alcoholic ammonia; although an 8-ring structure is a possible alternative, the constitution (XXXIV) has never been challenged. (A similar unsaturated structure is postulated for a compound prepared by Ruhemann and Allhusen.[59])

Cyclic Imides.

Of the 3- and 4-membered imides there are few if any authentic oxalimides. It does not seem possible to prepare the unsubstituted imide from oxamic acid, and the ethyl ester has given tetraketopiperazine.[60] Sabanéef's so-called phenyldicarbylamine, $PhNC_2$ (I), in its vigorous oxidation on exposure to air, is supposed to have given phenyloxalimide (oxanil), but there is little to prove its structure except that with water[61] the compound yields oxanilic acid. In this respect it differs considerably from the oxanil which Warren and Briggs[62] prepared from oxanilic acid by heating with thionyl chloride. The substance obtained by them is attacked only by concentrated sulphuric acid and alkaline reagents; it does not melt and has the low solubility of a polymer, despite the apparently normal molecular weight as determined in boiling nitrobenzene. The alcohol-soluble compound, m. p. 146°, described by A. G. Perkin[63] as 2 : 4 : 6-trinitro-oxanil, corresponds in properties much more closely with a simple cyclic imide.

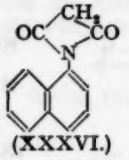
The action of boiling thionyl chloride on malonanilic acid is likewise said to give *N*-phenylmalonimide[62] (malonanil), another inert, high-melting solid, but the preparation of this

substance is proving difficult to repeat. It was hoped that malonimide might be prepared by hydrogenolysis of " malonylphenylhydrazine," a compound of m. p. 128° due to E. Fischer and Passmore.[64] It was said to be formed on heating at 200° the phenylhydrazine salt of the semiphenylhydrazide of malonic acid obtained on warming an aqueous acetic acid solution of phenylhydrazine and malonic acid.

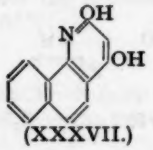
$$HO_2C\cdot CH_2\cdot CO_2H + 2NHPh\cdot NH_2 + AcOH\ aq.$$
$$\downarrow 100°$$
$$NHPh\cdot NH\cdot CO\cdot CH_2\cdot CO_2H, NHPh\cdot NH_2,\ m.\ p.\ 154°$$
$$\downarrow 200°,\ 15\ min.$$
$$H_2C(CO)_2N\cdot NHPh,\ m.\ p.\ 128°$$

The reputed imide was again mentioned in 1940 by Biquard and Grammaticakis,[65] but they failed to obtain the salt of m. p. 154°, the compound of m. p. 128° separating in its stead. This has since been confirmed, though the supposed imide has been identified as acetylphenylhydrazide, MeCO·NH·NHPh.[74] The salt, m. p. 154°, is obtained only if the acetic acid is omitted from the preparation, but no product other than acetylphenylhydrazide can be isolated from its pyrolysis.

By refluxing ethyl malonate with α-naphthylamine R. Meyer [66] obtained a crystalline solid to which he ascribed a malonimide structure (XXXVI). It was noticed that the conditions of its formation were not unlike those of 2 : 4-dihydroxy-7 : 8-benzquinoline (XXXVII) [67] and a comparison of the two products has now established their identity.[75]

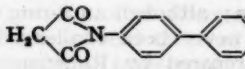


(XXXVI.)

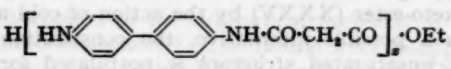


(XXXVII.)

This observation suggested a possible new structure for malonylbenzidine, first obtained by Remfry.[68] For the original multimembered ring, based on the Kaufler diphenyl structure, Le Fèvre [69] has substituted a malonimide formula (XXXVIII), characterised by an amorphous



(XXXVIII.)



(XXXIX.)

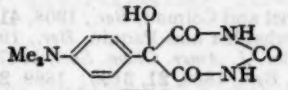
sulphate and a crystalline salicylidene derivative, m. p. 298—300°. Reinvestigation [74] of the sulphate discloses that the sulphur content varies with different preparations and is only a fraction of that required by the formula, $C_{15}H_{12}O_2N_2,H_2SO_4$. The derivative, m. p. *ca.* 300°, obtained from malonylbenzidine and salicylaldehyde by heating for a short time in phenol is heterogeneous, and contains disalicylidenebenzidine, m. p. 260°, which can be extracted with boiling benzene. After heating for 1¾ hours in phenol, almost the entire product is converted into disalicylidenebenzidine, m. p. and mixed m. p. 260°. The highly insoluble malonylbenzidine has all the characteristics of a polymeric substance (XXXIX), and there is no evidence to support the 4-ring-imide structure.

If on re-examination the small-ring imides seem to be a diminishing series, there remains one group, formed with remarkable ease, for which there is at least much circumstantial evidence.

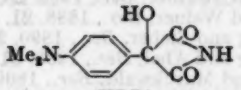
The first of these compounds was discovered long ago by Pellizzari [70] while investigating the condensation of alloxan with aromatic amines. When dissolved in dilute alkali, the resulting dialuric acids were decomposed with evolution of ammonia; typical of the products then precipitated on acidification is that from 5-*p*-dimethylaminophenyldialuric acid (XL), for which, among other possibilities, the structure (XLI) was proposed.

Dialuric acids of a similar nature, including many derived from phenols, are mentioned in several patents by Boehringer; [71] they are of interest as a source of aryltartronic acids, *e.g.*, (XLII), to which they are hydrolysed by boiling alkali. The supposed 4-ring imides

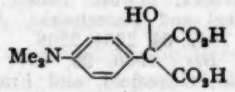
have not yet been degraded to tartronic acids, so that the isomeric 5-ring-imide (XLIII) formula can not be entirely excluded.



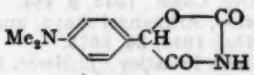
(XL.)



(XLI.)

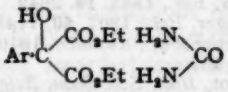


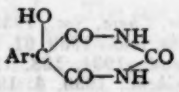
(XLII.)



(XLIII.)

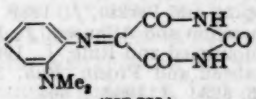
On the other hand, imides of apparently the same type have since been synthesised from various tartronic acids.[72] Ethyl esters of the tartronic acids were heated in alcoholic sodium ethoxide with urea, as in the standard pyrimidine synthesis, in the expectation that dialuric acids would be formed, but analyses indicated that the products were tartronic imides. This



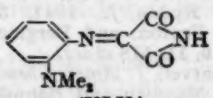


view was strengthened when the identical compounds were again obtained—though less successfully—on substituting ammonia for urea as the source of the imide nitrogen. The alternative 5-ring thus seems to be disproved, for it is difficult to imagine by what mechanism such a structure could be elaborated from a tartronic ester. Unfortunately, a direct comparison of the products obtained by the synthetic method with those from the alkaline hydrolysis of dialuric acids is not yet possible, as in no case have materials with the same aromatic substituents been used.

There is an apparent resemblance between the compounds just described and the imide which results from the hydrolysis of *o*-dimethylaminoaniline-alloxan anil (XLIV) with hot



(XLIV.)



(XLV.)

30% alkali.[73] The derivative is extraordinarily stable to hot concentrated alkalis and to hydrochloric acid, but its constitution as (XLV) is supported by analyses, determinations of molecular weight, and by a colour reaction with hydrogen peroxide and hydrochloric acid said to be specific for an *o*-dimethylamino-anil.

It is clear that there is still much to be learnt of the characteristics of the smaller ring systems. The further elucidation of their properties, and their examination by physico-chemical methods, may well lead to interesting progress in the chemistry of the heterocyclic compounds.

Added on March 24th, 1949.—Experiments completed (by Mr. J. W. C. Lewis) after the above account had been written show that the alkali-soluble hydrolysis product of 5-(2′ : 4′-dimethoxyphenyl)dialuric acid forms a monoacetate, and a monomethyl derivative insoluble in alkali and resistant to acetylation. This degradation product therefore appears to be 5-(2′ : 4′-dimethoxyphenyl)oxazolidine-2 : 4-dione, and despite indications to the contrary, *e.g.*, the synthetical work of Riebsohmer,[73] the existence of tartronic imides is thereby rendered improbable. It is significant that the so-called phenyltartronic imide [73] has m. p. 107·5—108°, a figure almost identical with that recorded for 5-phenyloxazolidine-2 : 4-dione (Traube and Ascher, *Ber.*, 1913, **47**, 2082). A further search instituted as a result of these observations has revealed that the alkali degradation products of some 5-substituted dialuric acids have in fact been identified synthetically as oxazolidinediones (Aspelund, *Acta Acad. Abœnsis Math. et Phys.*, 1939, **11**, No. 7, 4; 1939, **11**, No. 14, 3).

References.

[1] Ruzicka *et al.*, *Helv. Chim. Acta*, 1926, **9**, 499.
[2] Gabriel and Stelzner, *Ber.*, 1895, **28**, 2929.
[3] Gabriel and Weiner, *Ber.*, 1888, **21**, 2676.
[4] Ladenburg and Sieber, *Ber.*, 1890, **23**, 2727.
[5] Ladenburg and Abel, *Ber.*, 1888, **21**, 758.
[6] Howard and Marckwald, *Ber.*, 1899, **32**, 2031.
[7] Yanbikov and Dem'yanov, *Chem. Abs.*, 1939, **33**, 4583.
[8] Jones, *J. Org. Chem.*, 1944, **9**, 484.
[9] Likhosherstov, Arkhangel'skaya, and Shalaeva, *Chem. Abs.*, 1940, **34**, 3673.
[10] Kharasch and Priestley, *J. Amer. Chem. Soc.*, 1939, **61**, 3425.
[11] Karabinos and Serijan, *ibid.*, 1945, **67**, 1856; Campbell, Sommers, and Campbell, *ibid.*, 1946, **68**, 140.
[12] Freundlich and Salomon, *Ber.*, 1933, **66**, 355.
[13] Salomon, *Helv. Chim. Acta*, 1933, **16**, 1361.
[14] Private communication from Dr. Goodings, I.C.I. Ltd., Blackley; cf. Berchet, U.S.P. 2,212,146.
[15] Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 2328.
[16] Adams and Cairns, *ibid.*, 1939, **61**, 2464.
[17] Hoch, *Compt. rend.*, 1934, **198**, 1865; Campbell, *J. Org. Chem.*, 1939, **4**, 198; 1943, **8**, 99, 103; 1944, **9**, 185.
[18] Freundlich and Neumann, *Z. physikal. Chem.*, 1914, **87**, 69.
[19] Theunis, *Bull. Acad. roy. Belg.*, 1926, **12**, 785; de Booseré, *Bull. Soc. chim. Belg.*, 1923, **32**, 26.
[20] Corselli, *Gazzetta*, 1891, **21**, 271.
[21] Curtius and Dörr, *J. pr. Chem.*, 1930, **125**, 425.
[22] "Beilstein," 4th Ed., **22**, 117.
[23] Howard and Marckwald, *Ber.*, 1899, **32**, 2036.
[24] G. D. Jones *et al.*, *J. Org. Chem.*, 1944, **9**, 125.
[25] *Idem*, *ibid.*, p. 133; cf. Danehy and Pflaum, *Ind. Eng. Chem.*, 1938, **30**, 778.
[26] Hanby and Rydon, *J.*, 1947, 513 *et seq.*; Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, 1946, **11**, 518 *et seq.*
[27] Gibbs and Marvel, *J. Amer. Chem. Soc.*, 1935, **57**, 1137; Mannich and Baumgarten, *Ber.*, 1937, **70**, 210.
[28] Weissberger and Bach, *Ber.*, 1931, **64**, 1095; 1932, **65**, 631.
[29] Maitland, *Ann. Reports*, 1939, **36**, 239.
[30] Kincaid and Henriques, *J. Amer. Chem. Soc.*, 1940, **62**, 1474.
[32] Cairns, *loc. cit.*, 1941, **63**, 871.
[33] Pauling, Gilman's "Organic Chemistry," 1938, Vol. I, p. 334; cf. Tarbell and Fukushima, *J. Amer. Chem. Soc.*, 1946, **68**, 2499.
[34] W. Baker, *J.*, 1945, 258.
[35] Hollins, "Synthesis of Nitrogen Ring Compounds," 1924; Patterson and Capell, "The Ring Index," 1940, p. 32.
[36] Neber and Burgard, *Annalen*, 1932, **493**, 281; Neber and Huh, *ibid.*, 1935, **515**, 283.
[36] Wohl, *Ber.*, 1905, **38**, 4154; Voet, *Bull. Soc. chim.*, 1929, **45**, 61.
[37] Wohl, *Ber.*, 1901, **34**, 1914.
Richmond and Wright, *Canadian J. Res.*, 1945, **23**, 158.
[38] Gitsels and Wibaut, *Rec. Trav. chim.*, 1941, **60**, 50.
[40] Gabriel and Colman, *Ber.*, 1908, **41**, 513.
[41] Abderhalden and Paquin, *Ber.*, 1920, **53**, 1125.
[42] Gensler, *J. Amer. Chem. Soc.*, 1947, **69**, 1966.
[43] Paal, *Ber.*, 1888, **21**, 3190; 1889, **22**, 3076.
[44] Oesterreich, *Ber.*, 1897, **30**, 2254.
[45] A. Bowman, D.Phil. Thesis, Oxford, 1940; Frankel and Katschalski, *J. Amer. Chem. Soc.*, 1942, **64**, 2264, 2268.
[46] Leuchs, *Ber.*, 1906, **39**, 857; see also Katchalski, Grossfield, and Frankel, *J. Amer. Chem. Soc.*, 1948, **70**, 2094, for other references.
[47] L. G. Goldsworthy, F. E. King, and (Sir) R. Robinson, unpublished experiments, 1936—1939; Woodward and Schramm, *J. Amer. Chem. Soc.*, 1947, **69**, 1551; Astbury, Dalgliesh, Darman, and Sutherland, *Nature*, 1948, **162**, 596.
[48] Einhorn, *Ber.*, 1883, **16**, 2649.
[49] Staudinger, *Ber.*, 1907, **40**, 1145.
[50] Staudinger *et al.*, *Annalen*, 1910, **374**, 1; Merck, CPS, 483.
[51] Breckpot, *Bull. Soc. chim. Belg.*, 1923, **32**, 412; see also Pfizer, CPS, 156, 456; Merck, CPS, 421.
[52] Staudinger, *Ber.*, 1917, **50**, 1035.
[53] Gilman and Speeter, *J. Amer. Chem. Soc.*, 1943, **65**, 2255.
[54] A. H. Cook, *Quarterly Reviews*, 1948, **2**, 203; H. T. Clarke, J. R. Johnson, and (Sir) R. Robinson, "The Chemistry of Penicillin."
[55] Sheehan and Izzo, *J. Amer. Chem. Soc.*, 1948, **70**, 1985.
[56] Delépine, *Compt. rend.*, 1943, **216**, 785.
[57] Chain, *Endeavour*, 1948, **7**, 152; Chain, Philpot, and Callow, *Arch. Biochem.*, 1948, **18**, 171.
[58] Kipping and Perkin, *J.*, 1889, **55**, 339.
[59] Ruhemann and Allhusen, *J.*, 1894, **65**, 9.
[60] de Mouilpied and Rule, *J.*, 1907, **91**, 176.
[61] Sabaneéff and Prosin, *Bull. Soc. chim.*, 1901, **25**, 823; *A*, 1902, i, 604.
[62] Warren and Briggs, *Ber.*, 1931, **64**, 28.
[63] A. G. Perkin, *J.*, 1893, **63**, 1066.
[64] E. Fischer and Passmore, *Ber.*, 1889, **22**, 2735.
[65] Biquard and Grammaticakis, *Bull. Soc. chim.*, 1940, **7**, 766.
[66] R. Meyer, *Annalen*, 1906, **347**, 23.
[67] Baumgarten and Kärgel, *Ber.*, 1927, **60**, 832.
[68] Remfry, *J.*, 1911, **99**, 610.
[69] Le Fèvre, *J.*, 1929, 733.
[70] Pellizzari, *Gazzetta*, 1887, **17**, 412; 1888, **18**, 340; 1889, **19**, 397; 1911, **41**, 21; see also Széki, *Ber.*, 1923, **56**, 2464.
[71] Boehringer, "Friedländer," **5**, 117, 863; **6**, 158 *et seq.*
[72] Riebsohmer *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 3491.
[73] Rudy and Cramer, *Ber.*, 1938, **71**, 1234; *Oesterr. Chem.-Ztg.*, 1939, **42**, 329.
[74] F. E. King and J. R. Marshall, C. R. P. Morgan (Oxford), and J. W. C. Lewis, P. Smith (Nottingham), forthcoming publications.

ONE HUNDRED AND EIGHTH ANNUAL GENERAL MEETING.

THE One Hundred and Eighth Annual General Meeting of The Chemical Society was held at Burlington House on Thursday, March 31st, 1949, at 2.30 p.m. The President, Sir Ian Heilbron was in the Chair.

The notice convening the Meeting was read.

In presenting the Report of Council for 1948, copies of which were available, Sir John Simonson dealt briefly with the activities of the year in which the Society had made steady progress as was reflected in a continued growth of the Fellowship. He was able to report that the delay in publication was at last beginning to be reduced, and he hoped that, by the end of the year, this difficulty would largely be removed. He also referred to the valuable services which Dr. Driver had rendered to the Society as Editor.

Sir John Simonsen referred also to the encouraging increase in the number of meetings of the Society held throughout the Country during the year. The use of the Library by Fellows as well as by the Members of other Societies was steadily increasing, and more grants had been awarded from the Research Fund than for many years. The expansion in the activities of the Society, and the increasing popularity of its meetings had made the difficulties of accommodation even more acute during the past year than they had been before, and this matter had the Council's closest attention.

In dealing with the Accounts for 1948, the Treasurer stated that he had a less satisfactory state of affairs to describe. The published accounts showed a deficit for the year of over £1000, and this was after £2100 had been withdrawn from the Special Reserve for Publications against a total of £1300 placed to that Reserve in 1947. The increased expenditure was almost wholly due to the greatly increased cost of publication. The subscription had been increased in 1947 and the Council had asked that the contribution which Industry makes through the Chemical Council should be increased. An increased deficit in 1949 was inevitable but he hoped that the measures which were being taken would lead to more stable finances in subsequent years.

The Treasurer also referred to the arrangement whereby the Society, together with the Society of Chemical Industry, had come to an agreement with the Chemical Institute of Canada, which offered joint-membership of these three Societies to Canadian Chemists, on favourable terms.

In proposing the adoption of the Report of Council together with the Statement of Accounts and Balance Sheets for 1948, Dr. Neil Campbell referred especially to the generous consideration which the Council always gave to the problems of those Fellows who, although they lived at a distance, were enabled to take part in the activities of the Society. The motion was seconded by Dr. A. H. Lamberton, and the Report and the Accounts were adopted.

The following elections to vacancies on Council were announced :—

Honorary Secretary :

Professor Harold Burton.

Elected Ordinary Members of Council :

Constituency II :

Professor M. Stacey.

Constituency V :

Dr. E. G. V. Percival.

The report of the Scrutators on the ballot for Vice-Presidents who have not filled the Office of President, and for Elected Ordinary Members of Council for Constituencies I and III had been received, and it was declared that the following had been elected :—

Vice-Presidents who have not filled the Office of President:

Professor J. W. Cook.
Professor W. Wardlaw.

Elected Ordinary Members of Council:

Constituency I:

Dr. F. S. Dainton.
Dr. R. Spence.
Dr. A. I. Vogel.
Dr. J. Walker.
Dr. W. A. Waters.

Constituency III:

Professor C. E. H. Bawn.
Mr. J. D. Rose.

On the proposal of Professor C. W. Shoppee, seconded by Dr. G. Baddeley, Messrs. W. B. Keen & Co. were re-appointed Auditors for 1949.

A vote of thanks to the Officers and Council for their services during the past year was proposed by Professor E. R. H. Jones, who paid a tribute to the unsparing manner in which the Officers devoted their time to the Society's affairs and referred to the success which the difficulties imposed by the delays in publication were being tackled. He also paid a warm tribute to the work of the permanent staff of the Society. This vote of thanks was seconded by Dr. J. C. Withers and was accorded with acclamation.

Later in the afternoon, the Longstaff Medal for 1948 was presented to Sir Cyril Hinshelwood, Past President. After this ceremony, the President delivered his Presidential Address entitled "Concerning Amino-Acids, Peptides and Purines." At the conclusion of the Address, a vote of thanks proposed by Professor J. W. Cook was carried with enthusiasm.

The Anniversary Dinner, held at the Dorchester Hotel, was attended by two hundred and fifty Fellows and guests who were received by the President and Lady Heilbron, and by the Treasurer and the Senior Secretary. The Toast of "The Chemical Society" was proposed by Sir Edward Appleton, Secretary of the Department of Scientific and Industrial Research, and the President replied. Professor T. S. Wheeler proposed "The Guests," and replies were made by Professor G. Hevesy, Honorary Fellow, and by Lord Brabazon of Tara, President of the Royal Institution.

REPORT OF COUNCIL FOR 1948.

I. FELLOWSHIP.

1. *Fellowship Statistics.* On December 31st, 1948, the Register contained the names of 7875 Fellows, a net increase of 350 during the year. There were 732 elections to the Fellowship and 39 Fellows were reinstated. The Society has lost 66 Fellows by death, 216 by resignation, and 139 names were removed from the Register. Of the total Fellowship 4723 were Joint Members either of the Three Chartered Bodies or of the Chemical Society and the Society of Chemical Industry.

2. *Joint Student Facilities.* During 1948, 32 persons have been granted Joint Student Facilities by the two Societies under the Chemical Council Scheme.

3. *Honours.* The congratulations of the Society were conveyed to the following, whose names appeared in the lists of Birthday and New Year Honours:

Mr. C. A. Adams, C.B.E.
Dr. G. M. Bennett, C.B.
Mr. H. W. Cremer, C.B.E.
Professor A. Findlay, C.B.E.
Dr. C. R. Harington, Knight Bachelor.
Professor C. N. Hinshelwood, Knight Bachelor.
Sir James Irvine, K.B.E.
Dr. L. A. Jordan, C.B.E.
Dr. Alexander King, C.B.E.
Mr. R. O'F. Oakley, C.B.E.
Professor G. W. Robinson, C.B.E.

The Council has also congratulated Professor E. L. Hirst on the award of a Davy Medal by the Royal Society.

4. *Fellows who have completed 50 and 60 years of Fellowship.* Announcements have been made at Ordinary Scientific Meetings, and published in the *Proceedings*, of the congratulations of the Society that have been sent to those Fellows who during the year completed 60 years and 50 years of Fellowship.

5. *Deaths.* The Council learned with very deep regret of the death, on December 17th, 1947, of Johannes Nicolaus Brønsted, who was elected an Honorary Fellow in 1935. A resolution of sympathy was passed by the Council and transmitted to the Danish Chemical Society for communication to Professor Brønsted's relatives. The Council also regret to record the death of Dr. Bernard Dyer, who was elected to the Fellowship in 1875, and was, for a number of years, the senior Fellow of the Society.

The condolences of the Council have been conveyed to the relatives of those Fellows whom the Society has lost by death during the year.

6. *List of Fellows.* Arrangements have been made for the publication in 1949 of a list containing the names and addresses of Fellows. The list will be available from the General Secretary, price two shillings and sixpence.

II. PUBLICATIONS.

1. *Journal.* During the year, 548 scientific communications were received, of which 15 were declined and 2 were withdrawn. The *Journal*, which was larger than any previously published by the Society, comprised 535 items made up as follows:

Papers (General, Physical, and Inorganic)	124
,, (Physical Organic *)	16
,, (Organic)	326
Notes	45
Lectures and Addresses	5
Obituary Notices	17
Annual General Meeting	2

* Class first introduced in the December *Journal*.

Scientific communications published included contributions from Canada (2), Australia (13), New Zealand (14), South Africa (1), India (3), U.S.A. (2), Brazil (1), Egypt (15), France (2), Hungary (6), Netherlands (1), Norway (1), Palestine (2), Spain (1), Sweden (2), and Yugoslavia (1).

The following figures show the growth of publication during recent years:

	1944.	1945.	1946.	1947.	1948.
Scientific communications received	242	347	453	523	548
Published	199	262	278	375	511
Journal, pages	679	930	1175	1709	2330

These figures give only an imperfect idea of the very rapid increase in the rate of publication during the last months of 1948, since nearly two-thirds of the scientific communications published during that year appeared in the last six months. Towards the end of the year far more papers were being published than were being received, and it was estimated that, at the rate of publication then being achieved, papers received at the end of the year would be appearing in the July *Journal* of 1949.

Before the year ended arrangements had been made with Richard Clay and Company, Ltd., and the Cambridge University Press for the printing of a small supplementary volume of the *Journal* during 1949, and some of the work had been put in hand. It was estimated that this, together with the larger normal *Journal*, would end all serious delays in publication by the end of 1949.

2. *Annual Reports.* The *Annual Reports* for 1947 were published at the end of July, and were thus available to subscribers at a much earlier date than were the 1946 Reports in the previous year.

3. *Quarterly Reviews.* The demand for this publication continued to increase, and arrangements were made for reprinting Volume I which had sold out.

III. MEETINGS.

1. *Scientific Meetings.* The Society held 14 meetings in London during 1948. These included 8 lectures and 1 organised discussion. At the other 5 meetings 11 papers were read and discussed.

The number of meetings held outside London increased from 77 to 108. These included 98 lectures, 8 meetings for the reading of papers, and 1 conference. Two scientific film displays and a demonstration of research work were also held. Of these meetings 77 were held jointly with local sections of other bodies or with University Chemical Societies.

Official Scientific Meetings of the Society were held at Manchester on January 8th, at Dublin on March 2nd, and at Glasgow on December 3rd, 1948.

A complete list of meetings is given in Appendix A.

2. *Anniversary Meeting.* A report of the Anniversary Meeting held in Oxford on March 18th appeared in the *Journal* for April.

The Meeting consisted of the 107th Annual General Meeting, the Presidential Address, and the Anniversary Luncheon held in Oriel College. The Annual General Meeting was adjourned until June 3rd when the Accounts were approved. These Accounts were published in the *Journal* for June.

3. *Centenary Fund.* The income arising from the fund established at the time of the Society's Centenary has enabled the Society to arrange visits by chemists from overseas, who have been invited to lecture both in London and at other centres.

IV. LIBRARY.

The Annual Report of the Joint Library Committee for 1948 appears as Appendix B.

V. OTHER ACTIVITIES.

1. *Congratulations to His Majesty The King.* The loyal and dutiful congratulations of the Society were conveyed to His Majesty The King, Patron of the Society, on the occasion of the birth of H.R.H. Prince Charles of Edinburgh.

2. *Longstaff Medal.* The Longstaff Medal for 1948 has been awarded to Sir Cyril Hinshelwood.

3. *Harrison Memorial Prize.* The Harrison Memorial Prize for 1947 was awarded to Dr. H. R. Barton and was presented at the Anniversary Meeting.

4. *Grants for Research.* During the year the Council authorised the payment of research grants amounting to £887 to 37 applicants.

5. *Chemical Council.* Copies of the Report of the Chemical Council for 1947 may be obtained by Fellows on application to the General Secretary.

6. *Bureau of Abstracts.* The Report of the Bureau of Abstracts for 1947, which was not available for publication with the Report of Council for 1947, has now been issued. Copies of this, and of the Report of the Bureau for 1946, may be obtained from the General Secretary.

7. *Redecoration of the Society's Rooms.* The Council Room and the main staircase of the Society's premises in Burlington House were redecorated during the year.

8. *Accommodation.* The size of the attendance at meetings has made it necessary to hold lectures and discussions in London at halls with a larger seating capacity than that afforded by the Society's own Meeting Room.

In addition, accommodation has had to be found in Burlington House for the Editorial Staff of the Society. As a result of this measure, the Society's Rooms have not been available for meetings arranged by other societies. The Council very much regret the inconvenience caused to Fellows and to other societies by these difficulties which will, it is hoped, be overcome.

9. *International Exhibition of Pure and Applied Chemistry—Charleroi.* The publications of the Society were exhibited on a joint stand organised on behalf of a number of British societies connected with different branches of Chemistry.

VI. ADMINISTRATION.

1. *Personnel of Council.* At the Annual General Meeting held at Oxford on March 17th, the following were declared elected:

President	Sir Ian Heilbron.
Vice-Presidents	Mr. R. P. Bell, Dr. G. M. Bennett.
Treasurer	Sir Wallace Akers.
Honorary Secretary	Dr. Alexander King.
Ordinary Members of Council	Dr. L. L. Bircumshaw, Professor G. R. Clemo, Dr. A. H. Cook, Dr. A. E. Gillam, Dr. T. Malkin, Dr. S. Peat, Professor F. S. Spring, Dr. L. E. Sutton, Professor T. S. Wheeler.

The retirements of Mr. F. P. Dunn from the office of Treasurer and of Professor W. Wardlaw as Honorary Secretary were noted with special regret, and warm appreciation was expressed of the very valuable services they had rendered to the Society over a very difficult period.

During the year, the Council received with regret the resignation of a number of members who had moved out of their respective constituencies on taking up new appointments. In accordance with Bye-Law 42, the Council nominated the following to serve until the Annual General Meeting in 1949:

Dr. E. G. V. Percival appointed in place of Professor H. W. Melville.
Dr. F. S. Dainton appointed in place of Professor F. E. King.
Professor H. W. Melville appointed in place of Professor S. Peat.
Dr. J. Walker appointed in place of Professor C. W. Shoppee.

2. *Local Representatives.* The Council received with regret the resignation of Professor J. E. Coates and Professor F. E. King as Local Representatives for South Wales and Oxford respectively. Professor C. W. Shoppee and Dr. W. A. Waters were appointed in their place. Dr. J. C. Roberts was appointed Local Representative at Nottingham during the absence of Dr. D. O. Jordan in the U.S.A.

3. *Editors.* In December the Council learned with regret of the resignation of the Editor, Dr. J. E. Driver, who has been appointed Professor of Chemistry at the University of Hong Kong. Dr. L. C. Cross was appointed as Assistant Editor in August.

4. *Joint Subscription Scheme.* Certain modifications designed to simplify the collection of joint subscriptions for 1949, were made in co-operation with the Chemical Council and with the other societies concerned. In December, approval was given to an extension of the joint Subscription Scheme to include the Chemical Institute of Canada, for Fellows resident in Canada.

VII. FINANCE.

1. *Investments.* During the year a survey of the investments of the Society was made by a firm of stockbrokers with a view to securing the maximum income consistent with security for all the Funds. The Council accordingly rearranged the investments to ensure that at fixed intervals a certain proportion shall become due for redemption, thus providing regular opportunities for reinvestment in accordance with conditions prevailing at the date of repayment.

The Income of the Society derived from investments was reduced by some £70 as a result of the nationalisation of the railways.

Authority was given for the redemption of £200 3% Defence Bonds on Special Reserve Fund.

2. *Increased Prices of Publications.* To help meet the increased cost of printing and publication the Council has been obliged to increase to £5 per annum as from January 1st, 1949, the price at which the *Journal* is sold to non-Fellows.

3. *Contributions.* The Council records with thanks the following contributions towards the cost of publications:

£2500 from the Chemical Council.
£900 from the Government Scientific Publications Grant-in-Aid, distributed by the Royal Society.

Contributions of £25 from Mr. W. Collingwood Williams to mark his sixty years of Fellowship, and £10 from Dr. S. Horwood Tucker have also been gratefully received.

Further contributions amounting to £33 13*s.* 0*d.*, as already recorded in the *Proceedings*, have also been received for the Centenary Fund.

4. *Bequests.* The Society received the sum of £100 bequeathed under the will of the late Mr. Hugh Main. A legacy of £100 received under the will of the late Mr. George McGowan was spent on the purchase of books for the Library.

5. *Library.* Contributions have been received through the Chemical Council towards the maintenance of the Library from:

	£	*s.*	*d.*
The Royal Institute of Chemistry	1053	8	10
The Society of Chemical Industry	565	6	6
The Faraday Society	117	1	0
The Society of Public Analysts and Other Analytical Chemists	89	13	1
The Biochemical Society	117	1	0

6. *Staff Salaries.* Appropriate increases in salary have been granted to members of the Society's staff.

VIII. RELATIONS WITH OTHER BODIES.

1. *Representatives on Joint Committees and on Other Bodies.* The Society's representatives at December 31st, 1948, were as follows:

Association of British Chemical Manufacturers:

Joint Technical Committee on Patents: Dr. J. T. Hewitt.

Barker Committee:

Formed to support the publication of the Barker Index of the characteristic angles of crystalline compounds: Dr. G. M. Bennett.

Bristol University Court:

Professor F. G. Donnan.

British National Committee for Chemistry:

Sir Norman Haworth, Sir Ian Heilbron, Dr. W. H. Mills.

British National Committee for Crystallography:

Dr. G. M. Bennett.

British Standards Institution. Technical Committees:

Co-ordinating the work of the Divisional Councils in regard to any British Standard which may be issued in future for units, conversion factors, fundamental formulæ, values for properties of materials, etc.: Professor S. Sugden.
Standardisation of microchemical apparatus: Professor H. V. A. Briscoe, Dr. H. D. K. Drew.
Specifications for Materials and Plant used in Electroplating: Dr. U. R. Evans.
Standardisation of Scientific Glassware: Dr. G. R. Davies.
Standards for use in Dairying Chemistry: Mr. Eric Voelcker.
Standardisation of Letter Symbols: Professor S. Sugden
Technical Committee C/17 Viscosity: Dr. A. E. Dunstan.
Standardisation of the pH Scale: Professor H. T. S. Britton.

Bureau of Abstracts.

Directors and Members: Dr. G. M. Bennett, Mr. F. P. Dunn, Dr. E. B. Hughes, Dr. E. H. Rodd.
Members: Mr. R. P. Bell, Professor H. V. A. Briscoe, Dr. A. H. Cook, Professor W. Wardlaw.

Chemical Council:

Sir Wallace Akers, Professor D. H. Hey, Sir Cyril Hinshelwood, Dr. R. P. Linstead.

City and Guilds of London Institute:

Professor H. V. A. Briscoe.

Faraday Society—Colloid Committee:

Dr. G. S. Hartley.

Joint Library Committee:

Dr. H. Bassett, Dr. O. L. Brady, Dr. A. H. Cook, Dr. C. H. Desch, Mr. M. B. Donald, Professor H. J. Emeléus, Dr. P. Haas, Dr. T. A. Henry, Dr. J. R. I. Hepburn, Professor D. H. Hey, Professor E. D. Hughes, Dr. Harold King, Professor G. A. R. Kon, Professor E. E. Turner.

Lawes Agricultural Trust:

Committee of Management: Sir Norman Haworth.

Parliamentary and Scientific Committee:

Sir Ian Heilbron, Professor D. H. Hey.

Royal Society.

Joint Standing Committee for Symbols and Abbreviations: Professor C. W. Davies, Professor S. Sugden.

Yorkshire Council for Further Education:

Advisory Committee for Chemistry in South and East Yorkshire: Professor R. D. Haworth, Professor Brynmor Jones.

2. *Representatives of the Society at Conferences and Other Public Functions:*

Cuarto Congresso Sudamericano de Quimica: Professor J. W. Cook.

Installation of the Rt. Hon. The Viscount Halifax as Chancellor of the University of Sheffield, July 2nd: Professor R. D. Haworth.

XVIII International Geological Congress: Professor J. D. Bernal and Professor F. A. Paneth.

Royal Society, Scientific Information Conference, July 1948: Dr. G. M. Bennett.

Rubber Technology Conference, June 23rd—25th: Professor H. W. Melville.

100th Anniversary of the Death of Berzelius, Stockholm, September 1948: The President.

IX. ACKNOWLEDGMENTS.

The Council express their gratitude to those Fellows who have continued to give their services freely to the Society during the year. They would especially mention Local Representatives, Members of Committees, Referees of papers for the *Journal*, and those delivering lectures. The Council also deeply appreciated the generosity of those Fellows who have made gifts of the Society's publications, or of books, for the Library.

APPENDIX A.

MEETINGS HELD DURING 1948.

IN LONDON.

Unless otherwise stated all meetings were held in the Rooms of the Society at Burlington House.

January 8th, *Lecture*, "Structural Relationships in the Natural Unsaturated Higher Fatty Acids", by Professor T. P. Hilditch; January 22nd, *Meeting* for reading papers; February 5th, *Meeting* for reading papers; February 19th, *Sir Frederick Gowland Hopkins Memorial Lecture*, by Sir Edward Mellanby; March 4th, *Hugo Müller Lecture*, "The Occurrence and Significance of the Pentose Sugars in Nature, and their Relationship to the Hexoses", by Professor E. L. Hirst; April 22nd, *Meeting* for reading papers; May 6th, at the Royal Institution, *Lecture*, "The Molecular Orbital Theory of Valency", by Sir John Lennard-Jones; May 20th, *Victor Moritz Goldschmidt Memorial Lecture*, by Professor J. D. Bernal; June 3rd, at the Royal Institution, *Liversidge Lecture*, "The Modern Theory of Valency", by Professor L. C. Pauling; October 14th, *Meeting* for reading papers; October 28th, *Lecture*, "Strychnine, Brucine, and Vomicine", by Sir Robert Robinson; November 11th, *Tilden Lecture*, "The Structure and Reactivity of Free Radicals", by Professor C. E. H. Bawn; November 25th, at Imperial College of Science and Technology, *Discussion*, "The Theory and Practice of New Techniques in Separation and Purification", introduced by Dr. R. P. Linstead; December 9th, *Meeting* for reading papers.

OUTSIDE LONDON.

Aberdeen. Joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry: January 23rd, *Demonstration* of Current Research Work in the Chemistry Department, University of Aberdeen; at Marischal College: February 27th, *Lecture,* "Applications of Acetylenic Compounds in Organic Synthesis", by Dr. A. W. Johnson; March 24th, *Lecture,* "Some Stereochemical Problems", by Professor E. E. Turner; October 22nd, *Display of Scientific Films*; November 4th, *Lecture,* "Problems involved in the Generation of Useful Power from Nuclear Energy", by Sir Wallace Akers; December 10th, *Lecture,* "Macromolecular Adventures with the Electron Microscope", by Professor W. T. Astbury.

Birmingham. At the University: January 30th, *Lecture,* "Recent Developments in the Application of Infra-Red Spectroscopy to Chemical Problems", by Dr. G. B. B. M. Sutherland; March 1st, *Lecture,* "Steric Hindrance", by Professor C. K. Ingold; April 26th, *Lecture,* "Electron Transfer Reactions", by Professor M. G. Evans; (joint meetings with the University Chemical Society): May 24th, *Lecture,* "The Valency of Metals and the Structure of Intermetallic Compounds", by Professor L. C. Pauling; October 22nd, *Lecture,* "Cell Growth Phenomena and Chemical Kinetics", by Sir Cyril Hinshelwood; December 3rd, *Lecture,* "The Liquid State", by Dr. E. A. Moelwyn-Hughes.

Bristol. At the University: February 12th, *Lecture,* "The Formation of Ethylenic Polymers", by Professor H. W. Melville; November 4th (joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), *Lecture,* "Recent Advances in Chromatography", by Dr. T. I. Williams.

Edinburgh. At the North British Station Hotel (joint meetings with the local sections of the Royal Institute of Chemistry and Society of Chemical Industry), January 22nd, *Lecture,* "Some Recent Developments in Alkaloid Chemistry", by Dr. H. T. Openshaw; February 12th, *Lecture,* "The Chemistry of Rumination", by Dr. James Stewart: February 24th, at the University (joint meeting with the University Chemical Society), *Lecture,* "Proton Transfer and Analogous Reactions", by Professor W. F. K. Wynne-Jones: March 11th, at the North British Station Hotel (joint meeting with the local sections of the Royal Institute of Chemistry and Society of Chemical Industry), *Lecture,* "Practical Aspects of Wetting and Detergency", by Dr. E. S. Paice: April 20th, at the University, *Lecture,* "The Valency of Metals", by Professor L. C. Pauling: at the North British Station Hotel (joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry), October 21st, *Lecture,* "Some Aspects of the Chemistry and Biochemistry of Polycyclic Aromatic Hydrocarbons", by Professor J. W. Cook; November 18th, *Lecture,* "The Chemical Research Laboratory, Teddington", by Dr. R. P. Linstead; December 9th, *Lecture,* "Bread and its Influence on History", by Dr. D. W. Kent-Jones.

Eire. January 21st, at Trinity College, Dublin (joint meeting with the Irish Chemical Association), *Lecture,* "Santonin", by Professor Wesley Cocker; at University College, Dublin, February 27th (joint meeting with University College Chemical Society), *Lecture,* "Aromatic Nitration", by Professor C. K. Ingold; March 2nd, Official Meeting of the Society, *Pedler Lecture,* "Recent Developments in the Vitamin A Field", by Sir Ian Heilbron; at Trinity College, Dublin (joint meetings with the Werner Society), March 3rd, *Lecture,* "Recent Researches in the Azole Field", by Sir Ian Heilbron; May 28th, *Lecture,* "Absorption Spectra as Chemical Tools", by Dr. A. E. Gillam; July 1st, *Lecture,* "The Chemical and Biochemical Oxidation of Polycyclic Hydrocarbons", by Professor J. W. Cook; November 1st (joint meeting with University College Chemical Society and the Werner Society), *Lecture,* "Some Advances in the Chemistry of Fluorine", by Professor H. J. Emeléus; (Joint meetings with the Irish Chemical Association and Dublin Section of the Royal Institute of Chemistry) at University College, Dublin, November 2nd, at University College, Cork, November 4th, at University College, Galway, November 8th, "The Production and Uses of Radioactive Tracers", by Professor H. J. Emeléus; *Lecture,* November 12th, at Trinity College, Dublin (joint meeting with the University College

Chemical Society and the Werner Society), *Lecture*, " Some Properties of the Hydrogen Bond in Solids ", by Professor A. R. Ubbelohde.

Exeter. At Washington Singer Laboratories: February 2nd, *Lecture*, " Elucidation of the Structure of Penicillin ", by Professor W. Baker; February 21st, *Lecture*, " Some Reactions of Free Radicals ", by Dr. W. A. Waters; February 27th, *Lecture*, " Surface Films ", by Professor N. K. Adam; May 28th, *Lecture*, " Advances in Immunochemistry ", by Professor M. Stacey.

Glasgow. At the Royal Technical College: February 20th, Annual General Meeting of the Local Section followed by the reading of papers; March 12th, at the University, *Lecture*, " Some Problems in the Chemistry of Starch and Glycogen ", by Professor E. L. Hirst; October 29th, at the Royal Technical College (joint meeting with the Andersonian Chemical Society and the Glasgow University Alchemists Club), *Lecture*, " Chemical Personalities a Century Ago ", by Professor John Read; November 19th, at the University, *Tilden Lecture*, " The Structure and Reactivity of Free Radicals ", by Professor C. E. H. Bawn; December 3rd, at the Royal Technical College, Official Meeting of the Society, *Meeting* for reading papers.

Hull. At University College: January 30th (joint meeting with the local sections of the Oil and Colour Chemists Association and University College Scientific Society), *Lecture*, " Phthalocyanines and Related Recent Developments in Pigments ", by Dr. R. P. Linstead; February 19th (joint meeting with the Hull and District sections of the Royal Institute of Chemistry and University College Scientific Society), *Lecture*, " The Optical Properties of Molecules ", by Professor E. G. Cox ; May 20th (joint meeting with the University College Scientific Society), *Lecture*, " Kinetics of Some Organic Halogenation Reactions ", by Mr. R. P. Bell; October 21st (joint meeting with the local section of the Oil and Colour Chemists' Association and the University College Scientific Society), *Lecture*, " Surface Chemistry—its Achievements and its Future ", by Dr. A. E. Alexander; November 18th (joint meeting with the University College Scientific Society), *Lecture*, " The Preparation and Uses of Radioactive Isotopes ", by Professor H. J. Emeléus.

Leeds. At the University: March 2nd (joint meeting with the University Chemical Society), Display of Scientific Films followed by a *Lecture*, " The Protein Molecule and its Degradation by Enzymes ", by Dr. J. A. V. Butler; March 19th and 20th, Joint Conference of local societies, " Rheology in the Textile Industries "; May 3rd, *Lecture*, " The Valency of Metals and the Structure of Intermetallic Compounds ", by Professor L. C. Pauling; November 22nd, *Lecture*, " The Mechanism of Autoxidation ", by Professor C. E. H. Bawn.

Liverpool. At the University: February 19th (joint meeting with the local section of the Royal Institute of Chemistry), *Lecture*, " The Chemistry of Deterioration of Milk Powder ", by Dr. C. H. Lea; March 4th, *Tilden Lecture*, " Crystallographic Technique and its Chemical Significance ", by Professor E. G. Cox; March 16th, *Lecture*, " The Valency of Metals and the Structure of Intermetallic Compounds ", by Professor L. C. Pauling; (joint meetings with the local sections of the Royal Institute of Chemistry, the Society of Chemical Industry, and the British Association of Chemists), October 14th, *Lecture*, " The Preparation, Properties, and Handling of Elementary Fluorine ", by Dr. A. J. Rudge; November 10th, *Lecture*, " The Chemistry of some Carbohydrate Constituents of Bacteria ", by Professor M. Stacey; December 2nd, *Lecture*, " Modern Theories of Chemical Valency ", by Sir John Lennard-Jones.

Manchester. January 8th (joint meeting with the local sections of the Royal Institute of Chemistry and Society of Chemical Industry), at the University, *Lecture*, " Crystallisation of Fertilisers ", by Dr. M. P. Applebey; January 20th (joint meeting with the local sections of the Royal Institute of Chemistry and Society of Chemical Industry), at the Engineer's Club, *Lecture*, " Nitration by Mixtures of Nitric and Sulphuric Acids ", by Dr. G. M. Bennett; at the University, February 12th, Official Meeting of the Society and *Lecture*, " Some Problems in Nucleotide Synthesis ", by Professor A. R. Todd; April 8th, *Meeting* for reading papers; October 14th (joint meeting with the local sections of the Royal Institute of Chemistry and Society of Chemical Industry), *Lecture*, " Biochemistry of Vitamin A ", by Professor R. A. Morton; November 5th (joint meeting with

the local sections of the Royal Institute of Chemistry and Society of Chemical Industry), at the Engineer's Club, *Lecture*, " Studies in Australian Plant Chemistry ", by Professor John Read; at the University: November 11th, *Meeting* for reading papers; December 9th (joint meeting with the local sections of the Royal Institute of Chemistry and Society of Chemical Industry), *Lecture*, " Aromatic Nitration ", by Professor C. K. Ingold.

Newcastle and Durham. At King's College, Newcastle-on-Tyne: March 5th, *Meeting* for reading papers; April 23rd, *Bedson Club Lecture*, " The Valency of Metals and the Structure of Intermetallic Compounds ", by Professor L. C. Pauling; May 21st, *Bedson Club Lecture*, " Modern Theories of the Mechanism of Drug Action ", by Professor A. R. Todd; October 29th, *Bedson Club Lecture*, " Recent Work on Systems of Aromatic Type ", by Professor W. Baker; November 12th, *Meeting* for reading papers.

Northern Ireland. At Queen's University, Belfast: March 4th, *Pedler Lecture*, " Recent Developments in the Vitamin A Field ", by Sir Ian Heilbron; (Joint meetings with the Local Sections of the Royal Institute of Chemistry and Society of Chemical Industry), September 22nd, *Lecture*, " The Alumina and Aluminium Hydrate Industry ", by Mr. A. N. Adamson; at the Royal Belfast Academical Institution; October 5th, *Lecture*, " The Development of Chemical Institutions ", by Dr. H. J. T. Ellingham; December 1st (joint meeting with the local sections of the Royal Institute of Chemistry and Society of Chemical Industry), *Lecture*, " Some Chemical Aspects of Plastics Manufacture ", by Dr. R. G. R. Bacon.

North Wales. January 29th, at University College of North Wales, Bangor (joint meeting with the University College of North Wales Chemical Society), *Lecture*, " Reactions of the Ethylene Bond ", by Professor D. H. Hey; January 30th, at University College of Wales, Aberystwyth (joint meeting with the University College of Wales Chemical Society), *Lecture*, " Some Recent Advances in the Theory of Polymerisation ", by Professor D. H. Hey; at University College of North Wales, Bangor (joint meetings with the University College of North Wales Chemical Society), February 13th, *Lecture*, " Some Aspects of Solid Reactions ", by Professor W. E. Garner; November 25th, *Lecture*, " Problems in Inorganic Chemistry ", by Professor W. Wardlaw.

Nottingham. At the University (joint meetings with the University Chemical Society): January 22nd, *Lecture*, " Some Aspects of Aromatic Substitution ", by Professor Brynmor Jones; February 19th, *Lecture*, " The Application of Infra-Red Analysis to Problems in Molecular Structure ", by Dr. G. B. B. M. Sutherland; March 4th, *Meeting* for reading papers; November 18th, *Lecture*, " The Mechanism of Free-radical Reactions in Polymerisation ", by Professor M. G. Evans; December 9th, *Meeting* for reading papers.

Oxford. At the Physical Chemistry Laboratory, *Alembic Club Lectures*: May 10th, *Lecture*, " Some Recent Investigations of Natural Products ", by Professor R. D. Haworth; May 24th, *Lecture*, " Chemical Reactions induced by Nuclear Radiation ", by Dr. F. S. Dainton; June 7th, *Lecture*, " Exchange Reactions and Electrolytic Dissociation ", by Professor S. Sugden; October 18th, *Lecture*, " Aspects of Vapour-phase Oxidation ", by Dr. A. D. Walsh; November 1st, *Lecture*, " Some New Methods for the Preparation of Amidines ", by Dr. W. F. Short; November 15th, *Lecture*, " The Chemistry of Semiconducting Solids ", by Dr. J. S. Anderson.

St. Andrews and Dundee. At United College, St. Andrews: February 13th, *Lecture*, " Recent Developments in the Chemistry of Starch and Glycogen ", by Professor E. L. Hirst; April 21st, *Lecture*, " The Valency of Metals and the Structure of Intermetallic Compounds ", by Professor L. C. Pauling; at University College, Dundee (joint meeting with the Royal Institute of Chemistry and Society of Chemical Industry), December 10th, *Lecture*, " Problems of Biosyntheses ", by Professor J. N. Davidson.

Sheffield. At the University (joint meetings with the University Chemical Society): January 29th, *Lecture*, " Stereochemical Regularities in Catalytic Reactions ", by Dr. R. P. Linstead; February 12th, *Lecture*, " The Factors Influencing Radical Reactions in Solution ", by Professor M. G. Evans; November 4th, *Lecture*, " The Electron Microscope, and some Recent Discoveries with it in the Field of Macromolecules ", by Professor W. T. Astbury; November 18th, *Lecture*, " A Theory of Organic Reactions ", by Professor E. D. Hughes; December 2nd (joint meeting with the local section of the Royal Institute of

Chemistry and Sheffield University Chemical Society), *Lecture*, " Problems in the Production of Useful Power from Nuclear Energy ", by Sir Wallace Akers.

Southampton. January 23rd (joint meeting with the Southampton University College Chemical Society), at University College, *Lecture*, " Synthetic Organic Chemistry in Relation to Biology ", by Professor E. C. Dodds; March 12th (joint meeting with the University College Chemical and Physical Society), at University College, Southampton, *Lecture*, " Some Aspects of Infra-red Spectroscopy ", by Dr. G. B. B. M. Sutherland; May 21st (joint meeting with the Portsmouth and District Chemical Society), at Municipal College, Portsmouth, *Lecture*, " Cosmic Rays ", by Professor F. H. Newman; May 27th (joint meeting with the Chemical and the Physical Societies of University College), at University College, Southampton, *Lecture*, " Intermolecular Forces and Biological Specificity ", by Professor L. C. Pauling; October 19th (joint meeting with the Portsmouth and District Chemical Society), at Municipal College, Portsmouth, *Lecture*, " Tribochemistry and the Initiation of Explosives ", by Dr. F. P. Bowden; University College, Southampton, November 19th (joint meeting with the Mid-Southern Counties Section of the Royal Institute of Chemistry and University College of Southampton Chemical Society), *Lecture*, " Recent Advances in the Use of Organic Reagents in Analysis ", by Mr. G. H. Osborn; December 3rd (joint meeting with the University College of Southampton Chemical Society), *Lecture*, " Free Radical Mechanisms in the Initiation of Polymerisation Reactions ", by Professor M. G. Evans.

South Wales. At University College, Swansea: January 19th (joint meeting with the University College of Swansea Students' Chemical Society), *Lecture*, " The Physical Chemistry of Some Vacuum Metallurgical Processes ", by Dr. Philipp Gross; February 9th, *Lecture*, " Free-radical Reactions in Hydrocarbon Chemistry ", by Professor C. E. H. Bawn; March 5th (joint meeting with the University College of Swansea Students' Chemical Society), *Lecture*, " The Antibacterial Compound, Aspergillic Acid ", by Professor F. S. Spring; March 12th, at University College, Cardiff, *Lecture*, " The Contribution of the Organic Chemist to Medical Research ", by Professor C. R. Harington; November 15th (joint meeting with the University College of Swansea Students' Chemical Society), at University College, Swansea, *Lecture*, " The Structure of the Boron Hydrides and Similar Compounds ", by Mr. R. P. Bell; November 18th, at University College, Cardiff, *Lecture*, " The Chemistry of Penicillin ", by Professor Wilson Baker.

APPENDIX B.

ANNUAL REPORT OF THE JOINT LIBRARY COMMITTEE FOR THE YEAR 1948.

There was a slight decrease in the number of attendances by readers during the year. This is easily accounted for by the fact that the Reading Room was closed for a longer period than usual in the summer, when the staircase walls were being painted. The increasing value of the Library services is testified to both by letters and by comments from those using the Library in person and from those only able to do so by post.

Books issued, again show an increase, particularly in the case of those issued by post, all of which are registered.

The pressure on the photostat service has apparently been eased by the fact that the Science Library now undertakes copying, and is usually able to do it at a cheaper rate. The number of printed pages copied was 4605, a decrease of 435 on the previous year. Telephone enquiries dealt with again showed an increase, the respective figures for 1947 and 1948 being 1711 and 1764.

The number of books added to the Library was 282, of which 90 were presented. 583 volumes of periodicals were added, and 187 pamphlets. The total number of volumes in the Library is now 49,787, of which 15,054 are books and 34,733 volumes of periodicals.

Analysis.

	Attendances.	Books borrowed.	Books added.	Volumes of periodicals.	Pamphlets.
1948	11,547	9741 (3569 by post)	282	583	187
1947	11,710	9678 (3427 by post)	442	593	181

The number of books added shows a decrease because the books which were purchased in Germany by the BIOS team are included in the figure for 1947.

A thorough revision of the books in the Reading Room took place in the summer, and by sending over 1000 volumes to the basement stores the position on the shelves was eased, but the reserve space has been so severely reduced that the overall picture of accommodation is again becoming grave.

Some concern was caused by the sudden appearance of extensive mould on books in one of the Library stores. The Committee is most grateful to Messrs. R. Faraday Innes and A. J. Musgrave of the British Leather Manufacturers' Research Association and Dr. H. J. Plenderleith of the British Museum for their extensive researches into the cause of this attack and suggestions for its cure. Precautions recommended by them have been taken, which, it is hoped, will prevent any recurrence.

Books both new and historical have been presented to the Library by authors, publishers, and others, and the Society's collection of medals has also been enriched. To all the donors of such gifts the Committee desires to express its warm thanks.

INCOME AND EXPENDITURE GENERAL PURPOSES ACCOUNT FOR THE YEAR ENDED 31ST DECEMBER, 1948.

1947 £ s. d.	1947 £ s. d.	*Income.*	1948 £ s. d.	1948 £ s. d.
	284 13 1	To Life Composition Fees (£369 5*s.* 0*d.*), one-third as Income		123 1 8
		„ Annual Subscriptions:		
		Single-body Fellows—		
2462 6 2		Received in advance, on account of 1948	2858 0 11	
5780 17 5		Received during 1948 on account of 1948	6779 7 6	
307 16 6		Received during 1948 on account of 1947 and previous years	226 1 8	
		Joint Fellows—		
3210 19 3		Received in advance on account of 1948	2768 12 7	
7339 10 9		Received during 1948 on account of 1948	9024 17 10	
97 5 5		Received during 1948 on account of 1947 and previous years	146 12 6	
19,188 15 6			21,803 13 0	
		Add Payment from the Society of Chemical Industry to adjust cost of publications supplied to Joint Members	— — —	
765 10 0				
19,954 5 6			21,803 13 0	
		*Less** Contingent Liability to the Society of Chemical Industry to adjust cost of publications supplied to Joint Members	1000 0 0	
— — —				
19,954 5 6			20,803 13 0	
		Less Amount included in last year's Income, being valuation of Arrears as per last Balance Sheet	350 0 0	
350 0 0				
19,604 5 6			20,453 13 0	
		Add Arrears to date (£535) estimated to realise as per Balance Sheet	300 0 0	
350 0 0				
	19,954 5 6			20,753 13 0
	610 14 2	„ Dividends on Investments		541 5 7
	329 9 5	„ Income Tax recovered		289 14 5
	119 19 2	„ Donations		102 13 2
	— — —	„ Legacy—Hugh Main		100 0 0
	145 5 0	„ Miscellaneous Receipts		134 4 3
		„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet		1032 8 10
	— — —			
	£21,444 6 4			£23,077 0 11

1947 £ s. d.	1947 £ s. d.	*Expenditure.*	1948 £ s. d.	1948 £ s. d.
		By Administration Expenses:		
5365 17 0		Office Salaries and Wages	5891 2 5	
480 9 11		Superannuation	606 3 7	
649 6 3		House Expenses, etc.	1352 11 6	
126 0 0		Accountants' Charges	126 0 0	
872 16 10		Printing, Stationery, and Office Expenses...	932 8 4	
307 5 1		Postages...	281 13 7	
280 9 8		Furniture	107 7 2	
285 14 6		Miscellaneous...	312 15 6	
8367 19 3			9610 2 1	
		Less Transfer to Publications and Library:	£ s. d.	
821 17 7		Journal	1099 10 8	
160 12 4		Annual Reports	205 3 10	
160 12 4		Quarterly Reviews	205 3 10	
533 19 6		Library Account	244 14 11	
	6690 17 6		1754 13 3	7855 8 10
	380 4 8	„ Expenses on Account of Conjoint Chemical Office		658 1 9
	295 2 5	„ Expenses of Meetings		233 5 6
	30 5 0	„ Donations		31 10 0
	11,597 4 2	„ Balance of Expenditure on Publications to Publications Account		12,650 15 9
		„ Contribution to Library Account:		
438 2 1		For Fittings, Furniture, Books, Periodicals, and Binding	473 11 11	
500 9 8		Proportion of Maintenance...	547 17 10	
	938 11 9			1021 9 9
	800 0 0	„ Transfer to Special Reserve Fund: For Building Fund		— — —
	200 0 0	„ Transfer to Centenary Expenses Fund ...		— — —
	253 3 6	„ Expenses of Local Representatives		255 10 8
	3 13 6	„ Legal Charges		13 13 0
	215 4 8	„ Travelling Expenses of Members of Council		292 14 1
	34 13 7	„ Loss on Exchange (Australia)		64 11 7
	5 5 7	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet		— — —
	£21,444 6 4			£23,077 0 11

* The basis of adjustment for the years 1947 and 1948 has not yet been settled.

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1948.

PUBLICATIONS.

1947 £ s. d.	1947 £ s. d.	*Income.*	1948 £ s. d.	1948 £ s. d.
		To Publication Sales (including back numbers):		
6198 13 3		Journals and Proceedings	6820 3 11	
1368 6 10		Annual Reports on Progress of Chemistry	1236 16 4	
201 15 6		Quarterly Reviews	360 17 11	
588 10 3		Authors' Extra Reprints	670 6 11	
451 5 5		Abstracts (Back Nos. only 1944 and earlier)	390 6 5	
1 9 3		Collective Index (do.)...	15 3 2	
8 18 1		Other Publications	8 18 7	
	8818 18 7			9502 13 3
		„ Net Proceeds of Advertisements:		
991 7 7		Journal	1011 17 2	
77 0 0		Annual Reports	71 17 0	
	1068 7 7			1083 14 2
		„ Donations:		
	1750 0 0	Chemical Council		2500 0 0
		„ Government Publications Grant (through		
	900 0 0	the Royal Society)		900 0 0
		„ Cost of publishing Tilden Lectures:		
	25 4 0	Transfer from the Tilden Lecture Fund ...		— — —
	253 8 9	„ Dividends on Investments		206 7 7
	107 4 5	„ Income Tax recovered		107 4 0
	— — —	„ Transfer from Special Reserve Fund		2100 0 0
	— — —	„ Miscellaneous		12 0
		„ Transfer from General Purposes Account (the		
	11,507 4 2	balance of expenditure on publications)		12,650 15 9
	£24,523 7 6			£29,051 6 9

1947 £ s. d.	1947 £ s. d.	*Expenditure.*	1948 £ s. d.	1948 £ s. d.
		By Expenses on account of Journal:		
1584 14 7		Editorial Salaries	2185 16 8	
164 16 4		Superannuation	164 18 1	
61 16 9		Editorial Postages	70 17 8	
8651 19 9		Printing and Paper	12,706 7 7	
1728 15 9		Banding and Distribution	2235 9 1	
1152 11 9		Authors' Reprints	1246 2 6	
60 0 0		Indexing	60 0 0	
93 3 7		Furniture	78 10 4	
176 4 0		Miscellaneous	149 8 11	
821 17 7		Overhead Expenses (proportion)	1099 10 8	
	14,496 0 1			19,097 1 6
		„ Contributions to Bureau of Abstracts:		
	5500 0 0	Grants		5300 0 0
		„ Distribution of Abstracts (Back Nos. only		
	45 9 7	1944 and earlier)		63 1 11
	1300 0 0	„ Transfer to Special Reserve Fund		— — —
		„ Annual Reports on the Progress of		
		Chemistry:		
		Printing, Honoraria, Distribution,		
	1807 5 8	Authors' Copies, and Overhead Expenses		1899 13 11
		„ Quarterly Reviews:		
		Printing, Honoraria, Distribution,		
	1373 12 2	Authors' Copies, and Overhead Expenses		1791 9 5
	£24,523 7 6			£29,051 6 9

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1948.

LIBRARY.

1947 £ s. d.	1947 £ s. d.	*Income.*	1948 £ s. d.	1948 £ s. d.
		To Contribution for Fittings, Furniture, Books, Periodicals, and Binding:		
438 2 1		Transfer from General Purposes Account ...	473 11 11	
161 13 9		Transfer from Special Reserve Fund (deferred expenditure)	50 2 7	
— — —		Legacy—G. McGowan	100 0 0	
	599 15 10			623 14 6
		„ Contributions towards maintenance:		
		Through the Chemical Council:		
		Chemical Society (transfer from General Purposes Account)	547 17 10	
500 9 8		Royal Institute of Chemistry	1053 8 10	
962 17 7		Society of Chemical Industry	565 6 6	
516 16 0		Faraday Society	117 1 0	
108 16 0		Society of Public Analysts and other Analytical Chemists	89 13 1	
87 0 10		Biochemical Society	117 1 0	
— — —		From the Chemical Council	570 7 8	
564 8 2				3060 15 11
	2740 8 3			
		„ Contributions, etc., received from other sources towards maintenance:		
		Association of British Chemical Manufacturers	100 0 0	
100 0 0		Biochemical Society	— — —	
21 0 0		British Association of Chemists	— — —	
50 0 0		Institute of Brewing	50 0 0	
50 0 0		Society of Dyers and Colourists	10 10 0	
10 10 0		Miscellaneous receipts	56 13 5	
69 12 10				217 3 5
	301 2 10			
	£3641 6 11			£6901 13 10

1947 £ s. d.	1947 £ s. d.	*Expenditure.*	1948 £ s. d.	1948 £ s. d.
		By Capital and Extraordinary Expenditure:		
573 5 10		Books and Periodicals *	604 6 6	
26 10 0		Binding	19 8 0	
	599 15 10			623 14 6
		„ Maintenance:		
2151 15 0		Salaries and Wages	2616 10 4	
267 3 5		Superannuation of Library Staff	269 18 2	
49 4 6		Postages	49 16 4	
39 8 8		Miscellaneous Expenses	96 19 7	
533 19 6		Overhead Expenses (proportion)	244 14 11	
	3041 11 1			3277 19 4
	£3641 6 11			£3901 13 10

* Other than those received in exchange.

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1948.

SPECIAL RESERVE FUND.

1947			*Income.*	1948			1947			*Expenditure.*	1948		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
330	5	10	To Dividends on Investments	315	11	5	—	—	—	By Expenses on Change of Investments	219	19	10
17	4	6	„ Interest on Deposit	16	4	4	423	3	8	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	195	18	1
75	13	4	„ Income Tax recovered	84	2	2							
£423	3	8		£415	17	11	£423	3	8		£415	17	11

RESEARCH FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
394	4	11	To Dividends on Investments	356	4	5	385	0	0	By Grants	887	0	0
288	1	1	„ Income Tax recovered	280	16	7	—	—	—	„ Honorarium, Hugo Müller Lecture	21	0	0
—	—	—	„ Repayment of Grants	59	1	9	—	—	—	„ The Longstaff Medal	5	0	2
5	8	10	„ Interest on Deposit	5	15	9	2	19	9	„ Miscellaneous Expenses	15	19	8
—	—	—	„ Sale of Apparatus	17	19	0	367	15	1	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	—	—	—
68	0	0	„ Grants not claimed	30	0	0							
—	—	—	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet	179	2	4							
£755	14	10		£928	19	10	£755	14	10		£928	19	10

SPECIAL PUBLICATIONS FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
40	7	6	To Sales of Publications	35	12	10	—	—	—	By Cost of Record of Centenary Celebrations	425	6	0
74	0	8	„ Dividend on Investments	50	1	10	—	—	—	„ Cost of Binding Memorial Lectures, Vol. III	6	16	9
27	8	7	„ Interest on Deposit	28	1	3	10	11	0	„ Miscellaneous Expenses	2	9	0
—	—	—	„ Balance, being Excess of Expenditure over Income carried to Balance Sheet	320	15	10	131	5	9	„ „ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	—	—	—
£141	16	9		£434	11	9	£141	16	9		£434	11	9

INCOME AND EXPENDITURE ACCOUNTS OF OTHER FUNDS FOR THE YEAR ENDED 31ST DECEMBER, 1948.

STAFF PENSIONS FUND.

1947	*Income.*	1948	1947	*Expenditure.*	1948
£ s. d.		£ s. d.	£ s. d.		£ s. d.
103 11 5	To Dividends on Investments	79 4 11	840 0 0	By Pensions paid	840 0 0
25 12 4	„ Income Tax recovered	23 12 6			
16 4 10	„ Interest on Deposit	14 7 4			
694 11 5	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet	722 15 3			
£840 0 0		£840 0 0	£840 0 0		£840 0 0

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
29 15 5	To Dividends on Investments	28 5 0	— — —	By Harrison Prize	150 0 0
22 11 9	„ Income Tax recovered	22 11 10	4 10 0	„ Miscellaneous Expenses	2 2 0
6 9	„ Interest on Deposit	1 10		„ Balance, being Excess of Income over Expenditure, carried to Balance	
	„ Balance, being Excess of Expenditure over Income, carried to Balance		48 3 11	Sheet	— — —
— — —	Sheet	101 3 4			
£52 13 11		£152 2 0	£52 13 11		£152 2 0

SPECIAL LECTURES FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
35 1 6	To Dividends on Investment	17 10 9	25 0 0	By Honorarium	25 0 0
10 8 0	„ Income Tax recovered	10 8 0	— — —	„ Lecture Expenses	25 0 11
13 5	„ Interest on Deposit	13 7		„ Balance, being Excess of Income over Expenditure, carried to Balance	
	„ Balance, being Excess of Expenditure over Income, carried to Balance		21 2 11	Sheet	— — —
— — —	Sheet	21 8 7			
£46 2 11		£50 0 11	£46 2 11		£50 0 11

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1948.

THE FARADAY LECTURE FUND.

1947	*Income.*	1948	1947	*Expenditure.*	1948
£ s. d.		£ s. d.	£ s. d.		£ s. d.
7 4 3	To Dividends on Investment	7 4 4	25 0 0	By Honorarium	— — —
5 18 2	„ Income Tax recovered	5 18 3	3 5 0	„ Faraday Medal	— — —
5 0	„ Interest on Deposit	5 0	— — —	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	13 7 7
— — —	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet	— — —			
14 17 7		£13 7 7	£28 5 0		£13 7 7
£28 5 0					

THE TILDEN LECTURE FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
46 3 8	To Dividends on Investments	41 13 4	31 10 0	By Honorarium	15 15 0
27 9 10	„ Income Tax recovered	27 9 10	7 1 10	„ Lecture Expenses	5 11 2
3 0	„ Interest on Deposit	3 0	25 4 0	„ Transfer to Publications Account, for cost of publication of Lectures	— — —
			10 0 8	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	48 0 0
		£69 6 2	£73 16 6		£69 6 2
£73 16 6					

CENTENARY FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
33 11 2	To Dividends on Investments	175 0 8	61 19 1	By Expenses of Lecturers & Delegates	163 5 9
— — —	„ Income Tax recovered	54 6 0	7 11	„ Miscellaneous Expenses	4 3 0
	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet	— — —	— — —	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	61 17 11
28 15 10		£229 6 8	£62 7 0		£229 6 8
£62 7 0					

THE CHEMICAL SOCIETY.—BALANCE SHEETS, 31st December, 1948.

GENERAL PURPOSES.

1947 £ s. d.			*Liabilities.*	1948 £ s. d.		
	£	s. d.			£	s. d.
	5630	0 6	To Subscriptions received in advance ...		4,650	10 1
	9022	2 9	„ Sundry Creditors (Printing and other Expenses and Publications in advance)		10,445	12 0
22,718 4 11			„ Excess of Assets over Liabilities as per last Balance Sheet	23,374 10 0		
569 6 4			*Add* Life Composition Fees (£369 5*s.* 0*d.*) (two-thirds)	246 3 4		
81 13 2			*Add* net Profit on change of investment	1,502 12 10		
5 5 7			*Add* Excess of Income over Expenditure for year			
23,374 10 0				25,123 6 2		
			Deduct Excess of Expenditure over Income for year	1,032 8 10		
	23,374	10 0			24,090	17 4
	£38,026	13 3			£39,186	19 5

1947 £ s. d.		*Assets.*	1948 £ s. d.
27,234 4 7	By	Investments as per Schedule (cost or value when acquired)	28,736 17 5
4,482 0 7	„	Sundry Debtors	7,061 10 7
350 0 0	„	Subscriptions in Arrear (£535) estimated to realise	300 0 0
97 7 9	„	Stock of Paper (Journal, Annual Reports, and Quarterly Reviews)...	1,441 10 2
5,863 0 4	„	Cash at Bank and in hand	1,647 1 3
£38,026 13 3			£39,186 19 5

The Chemical Society. Balance Sheets, 31st December, 1948.

PUBLICATIONS FUND.

1947	*Liabilities.*		1948
£ s. d.		£ s. d.	£ s. d.
— — —	To Sundry Creditor	107 4 0	
9537 8 8	„ Excess of Assets over Liabilities as per last Balance Sheet	9708 10 6	
171 1 10	*Add* net profit on change of Investments	270 9 1	
£9708 10 6		£10,086 3 7	

1947	*Assets.*	1948
£ s. d.		£ s. d.
9708 10 6	By Investments as per Schedule (cost or value when acquired)	9978 19 7
— — —	„ Cash at Bank	107 4 0
£9708 10 6		£10,086 3 7

SPECIAL RESERVE FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.
	161 13 9	To Sundry Creditors		2150 2 7
		„ Reserve for Publications (including Quinquennial Index) as per last Balance Sheet	11,185 0 7	
9,885 0 7				
1,300 0 0		*Add* Amount transferred from Publications Account	— — —	
11,185 0 7			11,185 0 7	
— — —		*Deduct* Amount transferred to Publications Account	2,100 0 0	
	11,185 0 7			9085 0 7
		„ Reserve for Library Books and Binding as per last Balance Sheet	1,360 0 3	
1,821 14 0				
161 13 9		*Deduct* Amount transferred to Library Account for Books	50 2 7	
	1,360 0 3			1309 17 8
	3,350 0 0	„ Reserve for Research Fund as per last Balance Sheet		3350 0 0
		„ Emile Mond Bequest as per last Balance Sheet	— — —	
100 0 0				
100 0 0		*Deduct* Amount transferred to Centenary Fund	— — —	
	— — —			— — —
		„ Reserve for Building Fund	825 0 0	
25 0 0				
800 0 0		*Add* Amount transferred from General Purposes Account	— — —	
	825 0 0			825 0 0
		„ Excess of Income over Expenditure brought forward	1,858 7 0	
1,435 3 4				
423 3 8		*Add* Excess of Income over Expenditure for year	195 18 1	
1,858 7 0			2,054 5 1	
— — —		*Deduct* Net Loss on change of Investments	404 3 2	
	1,858 7 0			1650 1 11
	£18,740 1 7			£18,370 2 9

£ s. d.		£ s. d.
1,800 0 0	By Sundry Debtors (General Purposes and Publications Accounts) ...	— — —
16,162 10 2	„ Investments as per Schedule (cost or value when acquired)	14,558 7 0
777 11 5	„ Cash at Bank and on Deposit in London Savings Bank	3,811 15 9
£18,740 1 7		£18,370 2 9

RESEARCH FUND.

1947			*Liabilities.*			1948			1947			*Assets.*			1948		
£	s.	d.		£	s.	d.	£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.
			To Sundry Creditors				525	13	10	19,351	9	5	By Investments as per Schedule (cost or value when acquired)				19,492	17	3
20,116	14	5	„ Excess of Assets over Liabilities as per last Balance Sheet	20,727	3	4				1,738	13	8	„ Cash at Bank (including Deposit) and on deposit in Post Office Savings Bank				1,722	5	5
242	13	10	*Add* net Profit on change of Investments	141	7	10													
367	15	1	*Add* Excess of Income over Expenditure for year	—	—	—													
20,727	3	4		20,868	11	2													
—	—	—	*Deduct* Excess of Expenditure over Income for year	179	2	4													
			20,727 3 4				20,689	8	10										
			£21,090 3 1				£21,215	2	8	£21,090	3	1					£21,215	2	8

SPECIAL PUBLICATIONS FUND.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.	£	s.	d.		£	s.	d.
			14	8	To Sundry Creditors				3	3	3	20	11	4	By Sundry Debtors				23	9	10
					„ Excess of Assets over Liabilities as per last Balance Sheet	3116	1	11				1600	0	0	„ Investment as per Schedule (cost or value when acquired)				2011	19	10
2984	16	2													„ Cash at Bank (including Deposit) and on deposit in the Post Office Savings Bank and London Savings Bank						
—	—	—	*Add* Net Profit on change of Investments ...	411	19	10				1496	5	3					1174	19	6
131	5	9	*Add* Excess of Income over Expenditure for year	—	—	—													
3116	1	11		3528	1	9													
—	—	—	*Deduct* Excess of Expenditure over Income for year	320	15	10													
			3116 1 11				3207	5	11										
			£3116 16 7				£3210	9	2	£3116	16	7					£3210	9	2

STAFF PENSIONS FUND.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.	£	s.	d.		£	s.	d.
						To Excess of Assets over Liabilities as per last Balance Sheet	5863	6	7				4247	13	9	By Investments as per Schedule (cost or value when acquired)				4165	17	6
6537	17	9													„ Cash at Bank (including Deposit) and on deposit in the Post Office Savings Bank						
20	0	3	*Add* Profit on redemption of Investment	—	—	—							1615	12	10		892	17	7
6557	18	0		5863	6	7													
—	—	—	*Deduct* Net Loss on change of Investments	81	16	3													
694	11	5	*Deduct* Excess of Expenditure over Income for year	722	15	3													
			5863 6 7				5058	15	1										
			£5863 6 7				£5058	15	1	£5863	6	7					£5058	15	1

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

1947			*Liabilities.*	1948			1947			*Assets.*	1948		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
1199	19	2	To Excess of Assets over Liabilities as per last Balance Sheet	1248	3	1	1101	7	11	By Investments as per Schedule (cost or value when acquired)	1101	7	11
48	3	11	*Add* Excess of Income over Expenditure for year				146	15	2	„ Cash at Bank	45	11	10
1248	3	1		1248	3	1							
			Deduct Excess of Expenditure over Income for year	101	3	4							
						1146	19	9					
		1248	3	1		£1146	19	9	£1248	3	1		£1146	19	9
		£1248	3	1									

SPECIAL LECTURES FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
1217	1	7	To Excess of Assets over Liabilities as per last Balance Sheet	1238	4	6	1000	0	0	By Investment as per Schedule (cost or value when acquired)	1365	5	0
21	2	11	*Add* Excess of Income over Expenditure for year				238	4	6	„ Cash at Bank (including Deposit)	216	15	11
			Add Net Profit on change of Investments	365	5	0							
1238	4	6		1603	9	6							
			Deduct Excess of Expenditure over Income for year	21	8	7							
						1582	0	11					
		1238	4	6		£1582	0	11	£1238	4	6		£1582	0	11
		£1238	4	6									

THE FARADAY LECTURE FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
472	3	9	To Excess of Assets over Liabilities as per last Balance Sheet	457	6	2	369	4	0	By Investment as per Schedule (cost or value when acquired)	369	4	0
			Add Excess of Income over Expenditure for year	13	7	7	88	2	2	„ Cash at Bank (including Deposit)	101	9	9
472	3	9		470	13	9							
14	17	7	*Deduct* Excess of Expenditure over Income for year										
						470	13	9					
		457	6	2		£470	13	9	£457	6	2		£470	13	9
		£457	6	2									

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1948.

THE TILDEN LECTURE FUND.

1947			*Liabilities.*	1948			1947			*Assets.*	1948		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			To Creditor		25	4 0							
			„ Excess of Assets over Liabilities as per last Balance Sheet	1966	2	3	1878	14	10	By Investments as per Schedule (cost or value when acquired)	1878	14	10
1956	1	7											
10	0	8	*Add* Excess of Income over Expenditure for year	48	0	0	112	11	5	„ Cash at Bank (including Deposit)	160	11	5
				2014	2	3							
		1966	2 3								£2039	6	3
		£1991	6 3		£2039	6 3	£1991	6	3				

CENTENARY FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			To Sundry Creditors										
		50	7 0										
			„ Capital Account:										
			Contributions under Deeds and Donations brought forward	11,727	7	1							
11,841	17	7	*Add* Contributions under Deeds and Donations for year	3,198	18	11							
—	—	—		14,926	6	0							
11,841	17	7											
—	—	—	*Deduct* Net Loss on change of Investments	301	16	8							
			Deduct Expenses of Appeal and Inland Revenue Stamps	—	—	—							
114	10	6		14,624	9	4							
		11,727	7 1										
—	—	—	„ Excess of Income over Expenditure for year	61	17	11							
—	—	—	*Deduct* Excess of Expenditure over Income brought forward	28	15	10							
				33	2	1							
				£14,657	11	5	£11,777	14	1		£14,657	11	5
		£11,777	14 1										

SCHEDULE OF INVESTMENTS.

GENERAL PURPOSES.

Nominal Details.	*Cost or Value when Acquired.*	*Market Value 31st December 1948.*
	£ s. d.	£ s. d.
£2426 15s. 0d. 3½% Conversion Loan, 1961, or after	1884 12 8	2584 9 9
£2408 2s. 6d. 3% Funding Loan, 1959/69	2429 11 5	2504 9 0
£2400 14s. 9d. 3% Savings Bonds, 1960/70	2418 11 0	2484 15 3
£2000 3% Savings Bonds, 1965/75	2006 4 5	2060 0 0
£4490 19s. 8d. 3% British Transport Guaranteed Stock, 1978/88 ...	5444 14 11	4513 8 9
£2546 1s. 4d. 3% British Electricity Guaranteed Stock, 1968/73 ...	2549 4 5	2622 9 0
£1200 2½% Defence Bonds	1200 0 0	1200 0 0
£2400 2½% Bristol Corporation Debenture Stock, 1957	2070 2 0	2328 0 0
£1550 3½% London County Consolidated Stock, 1954/59	1639 2 6	1604 5 0
£2000 3% London County Consolidated Stock, 1962/67	2032 10 0	2070 0 0
£2500 3% Commonwealth of Australia Registered Stock, 1964/66 ...	2509 7 6	2575 0 0
£A2170 4% Commonwealth of Australia Treasury Bonds, 1961 ...	1833 13 0	1805 8 10
£A830 4% Commonwealth of Australia Treasury Bonds, 1961 ...	719 3 7	690 10 0
	£28,736 17 5	£29,042 15 7

PUBLICATIONS FUND.

£9260 19s. 9d. 3½% Conversion Loan, 1961, or after	1566 16 4	2407 19 0
£1000 3% Savings Bonds, 1955/65	1000 0 0	1045 0 0
£2261 1s. 11d. 3% Savings Bonds, 1960/70	2276 1 11	2340 4 8
£2175 13s. 4d. 3% British Transport Guaranteed Stock, 1978/88 ...	1929 1 4	2186 10 11
£2000 3% British Electricity Guaranteed Stock, 1968/73	2002 10 0	2060 0 0
£1200 3% Commonwealth of Australia Registered Stock, 1964/66 ...	1204 10 0	1236 0 0
	£9978 19 7	£11,275 14 7

SPECIAL RESERVE FUND.

£1300 2½% Defence Bonds	1300 0 0	1300 0 0
£2400 2½% National War Bonds, 1949/51	2400 0 0	2418 0 0
£3700 2½% National War Bonds, 1952/54	3700 0 0	3820 5 0
£1500 3% Savings Bonds, 1955/65	1500 0 0	1567 10 0
£2582 10s. 9d. 3% Liverpool Corporation Stock, 1955/58	2647 2 0	2672 18 6
£3000 2½% Funding Loan, 1956/61	3011 5 0	3060 0 0
	£14,558 7 0	£14,838 13 6

RESEARCH FUND.

£4177 16s. 1d. 3½% Conversion Loan, 1961, or after	3625 16 8	4449 7 3
£500 Defence Bonds, 4th Issue	500 0 0	500 0 0
£4000 3% Savings Bonds, 1960/70	4060 0 0	4140 0 0
£3755 2s. 1d. 3% British Transport Guaranteed Stock, 1978/88 ...	3567 19 5	3773 17 7
£3719 8s. 2d. 3% British Electricity Guaranteed Stock, 1968/73 ...	3724 1 2	3830 19 9
£4000 3% Commonwealth of Australia Registered Stock, 1964/66 ...	4015 0 0	4120 0 0
	£19,492 17 3	£20,814 4 7

SPECIAL PUBLICATIONS FUND.

Nominal Details.	*Cost or Value when Acquired*	*Market Value 31st December, 1948.*
	£ s. d.	£ s. d.
£715 8s. 10d. 3½% Conversion Loan, 1961, or after	541 2 4	761 18 11
£746 1s. 0d. 3% British Transport Guaranteed Stock, 1978/88 ...	719 18 9	749 15 7
£750 3% British Electricity Guaranteed Stock, 1968/73	750 18 9	772 10 0
	£2011 19 10	£2284 4 6

STAFF PENSIONS FUND.

£683 6s. 1d. 3½% Conversion Loan, 1961, or after	527 13 9	727 14 4
£150 2½% National War Bonds, 1951/53	150 0 0	153 15 0
£170 3% Savings Bonds, 1955/65	170 0 0	170 0 0
£815 2s. 7d. 2½% Funding Loan, 1956/61	818 3 9	831 8 7
£2500 2½% Defence Bonds	2500 0 0	2500 0 0
	£4165 17 6	£4382 17 11

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£61 15s. 8d. 3½% Conversion Loan, 1961, or after	50 1 5	65 15 11
£1489 10s. 6d. 3% British Transport Guaranteed Stock, 1978/88 ...	1051 6 6	1496 19 5
	£1101 7 11	£1562 15 4

SPECIAL LECTURES FUND.

£1414 15s. 3d. 3% British Transport Guaranteed Stock, 1978/88 ...	£1365 5 0	£1421 16 8

THE FARADAY LECTURE FUND.

£374 19s. 0d. 3½% Conversion Loan, 1961, or after	£369 4 0	£399 6 5

THE TILDEN LECTURE FUND.

£419 4s. 10d. 3% Funding Loan, 1959/69	386 12 10	436 0 3
186 National Provincial Bank Shares £5 each, £1 paid "B"	678 18 0	744 0 0
£681 19s. 1d. 3% British Transport Guaranteed Stock, 1978/88 ...	625 2 0	685 7 3
£220 3% Metropolitan Water Board (Kent Water Works) Deb. Stock	188 2 0	220 0 0
	£1878 14 10	£2085 7 6

CENTENARY FUND.

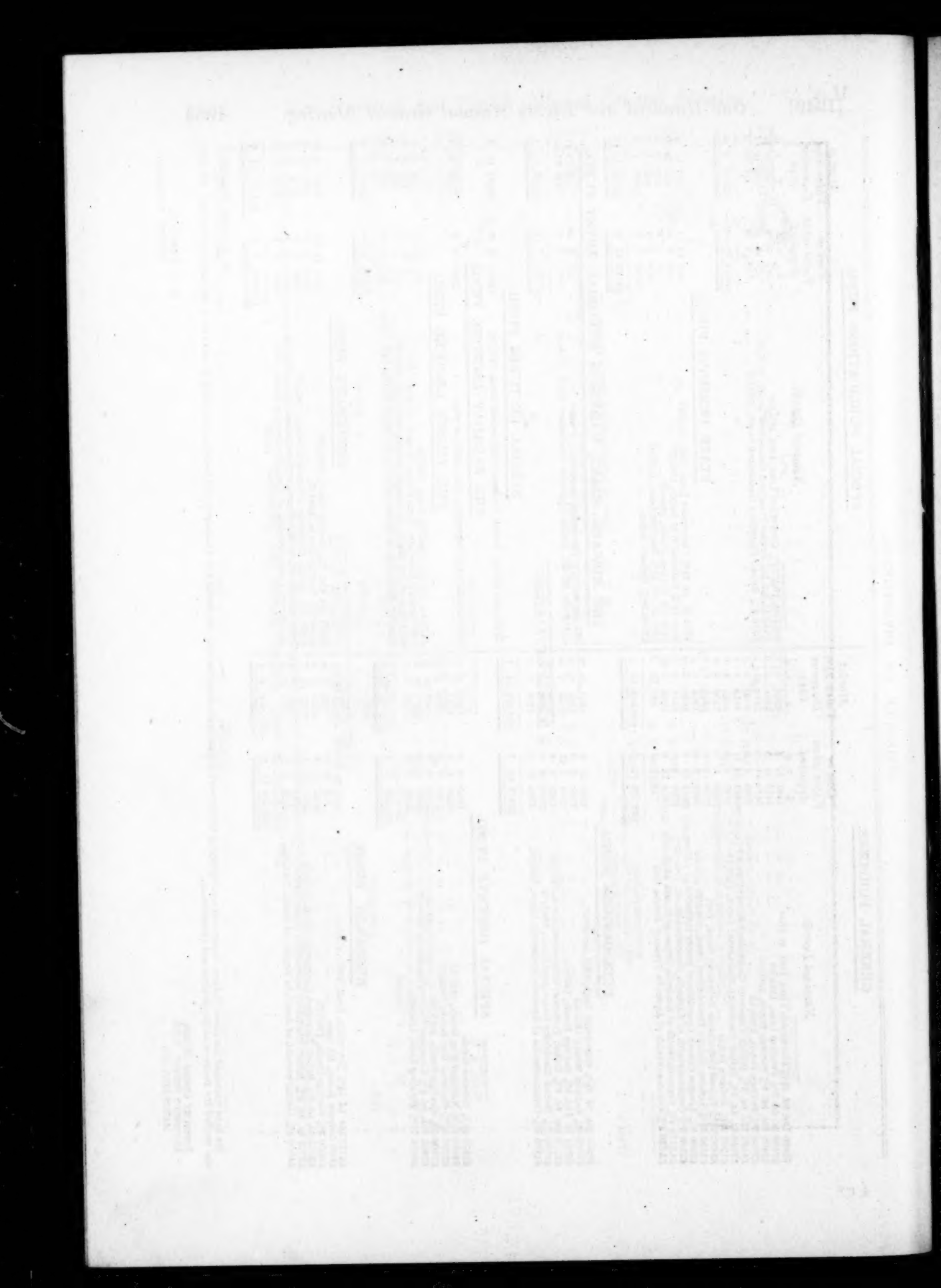
£2477 13s. 11d. 3% Savings Bonds, 1955/65	2491 11 10	2589 3 10
£2500 3% Savings Bonds, 1960/70	2534 7 6	2587 10 0
£2500 3% British Electricity Guaranteed Stock, 1968/73	2498 8 9	2575 0 0
£2279 15s. 0d. 3% British Transport Guaranteed Stock, 1978/88 ...	2237 7 9	2291 0 11
£A3500 4% Commonwealth of Australia Treasury Bonds, 1961 ...	2936 7 6	2912 0 0
	£12,698 3 4	£12,954 14 9

W. A. AKERS, *Treasurer.*

We have examined the above Balance Sheets and accompanying Income and Expenditure Accounts with the Books and Vouchers of the Society, and certify them to be in accordance therewith. We have also verified the Balances at the Bankers and Investments.

FINSBURY CIRCUS HOUSE,
BLOMFIELD STREET, E.C.2.
MARCH 21ST, 1949.

W. B. KEEN & CO.
Chartered Accountants.



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